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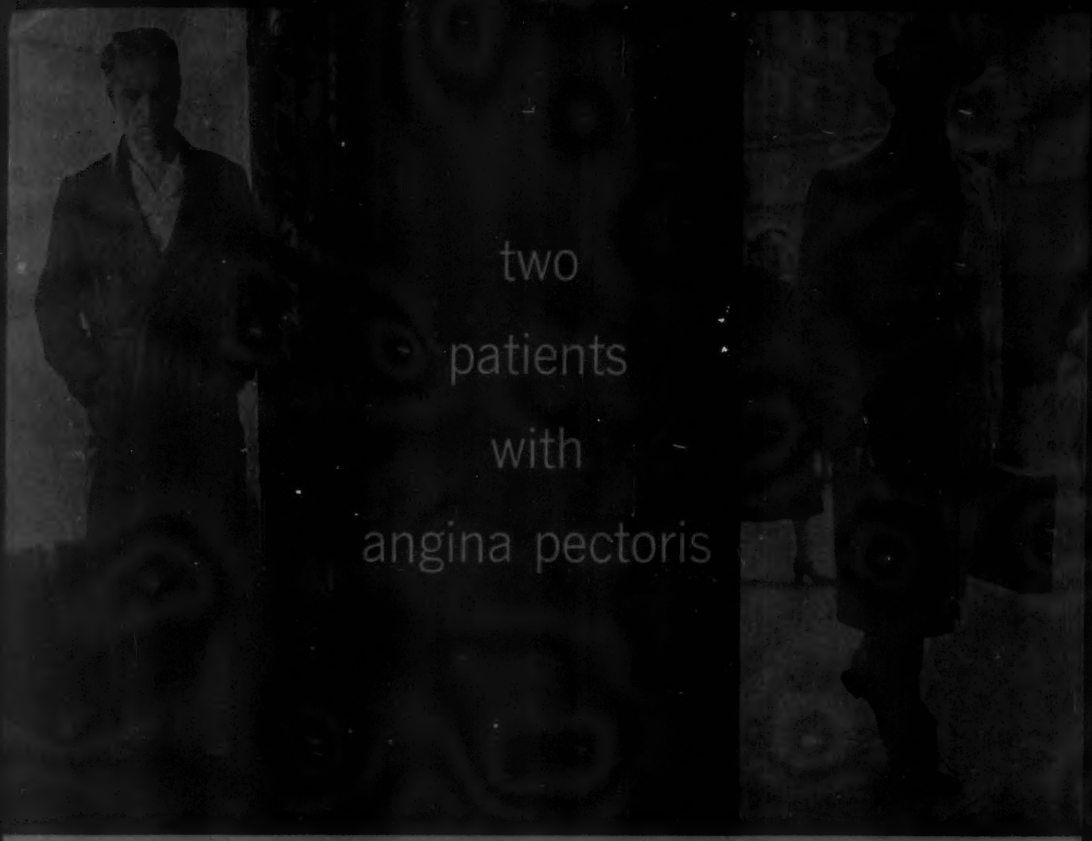
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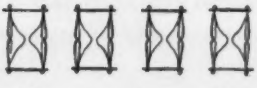
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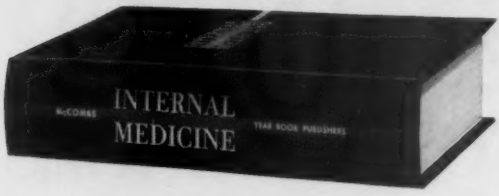
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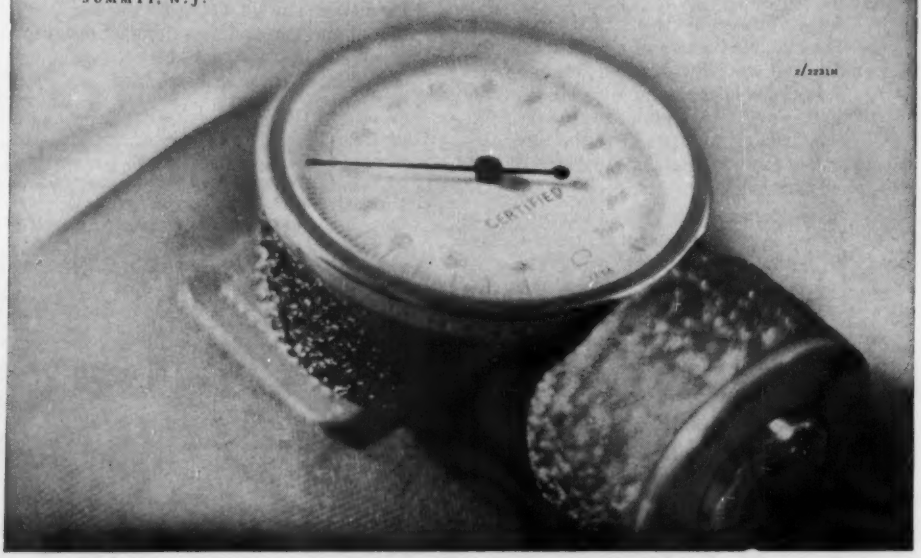
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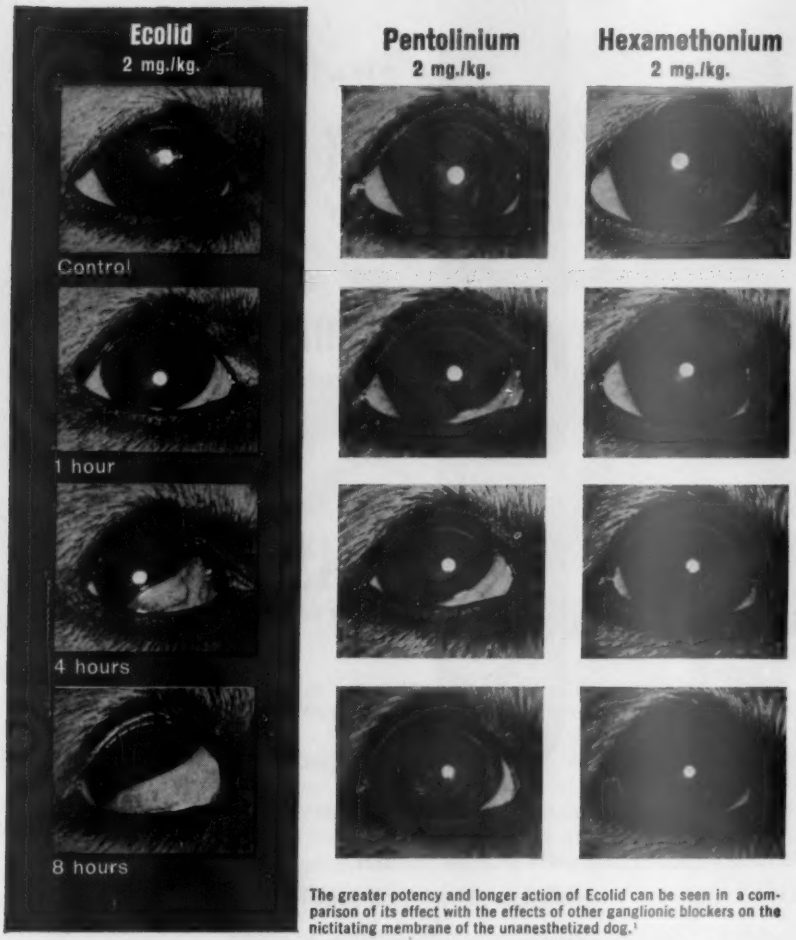
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Tuition fees for all courses will be: Members, $30.00; Non-members, $60.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.

recognized

as a potent, specific anti-arthritic

established

by over 100 million patient days

substantiated

in more than 700 published reports

BUTAZOLIDIN®

(phenylbutazone GEIGY)

potent, specific anti-arthritic

Based on an impressive background of achievement attained over a period of four years involving both long-term and short-term therapy in all the major forms of arthritis, BUTAZOLIDIN is recognized as one of the most effective anti-arthritic agents currently available.

relieves pain

improves function

resolves inflammation

BUTAZOLIDIN being a potent therapeutic agent, physicians unfamiliar with its use are urged to send for literature before prescribing it.

GEIGY

GEIGY PHARMACEUTICALS, Division of Geigy Chemical Corporation, New York 13, N. Y.

Combined for a new resistant

new METRETON *tablets*

METICORTEN (PREDNISONE) PLUS CHLOR-TRIMETON WITH ASCORBIC ACID

For prompt and effective relief, especially in many resistant allergic disorders, METRETON affords the benefits of two established agents with unexcelled anti-inflammatory, anti-allergic and antipruritic effectiveness. ***supported by essential vitamin C***—for stress support and for postulated effect on prolonging steroid action ***no better corticosteroid***—original brand of prednisone...minimal electrolyte effects—METICORTEN ***no better antihistamine***—unexcelled in potency and freedom from side effects—CHLOR-TRIMETON effective against hay fever, pollen asthma, perennial rhinitis, acute and chronic urticaria, angioneurotic edema, drug reactions, inflammatory and allergic eye disorders, pruritic and contact dermatoses.

formula: Each tablet of METRETON provides 2.5 mg. of METICORTEN (prednisone), 2 mg. of CHLOR-TRIMETON maleate (chlorprophenpyridamine maleate), and 75 mg. ascorbic acid.

supplied: METRETON Tablets, bottles of 30 and 100.

frontal attack

allergies

new

METRETON *nasal spray*

METICORTELONE (PREDNISOLONE) PLUS CHLOR-TRIMETON

quickly clears nasal passages • avoids rebound engorgement and sympathomimetic side effects • safe even for cardiacs, hypertensives, children, pregnant patients •

Composition: Contains 2 mg. (0.2%) METICORTELONE acetate (prednisolone acetate) and 3 mg. (0.3%) of CHLOR-TRIMETON gluconate (chlorprophenpyridamine gluconate) in each cc.

Packaging: 15 cc. plastic "squeeze" bottle, box of 1.

METRETON,* brand of corticoid-antihistamine compound; METICORTEN,* brand of prednisone; METICORTELONE,® brand of prednisolone; CHLOR-TRIMETON,® brand of chlorprophenpyridamine preparations. *T.M.

MT-J-576



Schering

Medihaler
Means self-powered, uniform, measured-dose inhalation therapy...

Medihaler
Means true nebulization. Each measured dose provides 5 to 8 times as many particles in the ideal size range as conventional nebulizers...

Medihaler
Means an unbreakable Oral Adapter—no movable parts—no glass to break—no rubber to deteriorate...

Medihaler
Means effective medications in an inert aerosol vehicle, in leakproof, spillproof, plastic-coated bottles...

Medihaler
Means utmost patient convenience—medication and Adapter together in plastic case, convenient for pocket or purse...

Medihaler
Means greater economy—no costly glass nebulizers to replace, and one inhalation usually suffices for prompt relief.

Medihaler®
THE UNIQUE MEASURED-DOSE INHALATION METHOD

In Asthma
For Rapid Relief of Acute or Continuing Bronchospasm

℞ Medihaler-Epi™
Riker brand of epinephrine 0.5% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.125 mg. epinephrine. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

℞ Medihaler-Iso™
Riker brand of isoproterenol HCl 0.25% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.06 mg. isoproterenol. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Medihaler-Epi replaces injected epinephrine in emergency situations in which respirations have not ceased. It provides rapid relief in acute food, drug, or pollen reactions (including urticaria, bronchospasm, angioneurotic edema, edema of glottis, etc.). In most instances only one inhalation is necessary.

℞ Medihaler Oral Adapter

Note: First prescription for Medihaler medications should include the desired medication and Medihaler Oral Adapter.

Oral Adapter made of hard plastic with no movable parts...foolproof...unbreakable and easily cared for by rapid rinsing...entire set, including medication, fits into neat plastic case small enough to be carried inconspicuously in pocket or purse...the smallest package for nebulization ever produced.



In Angina Pectoris
NEW Medihaler-Nitro™
Medihaler-Nitro is 1% octyl nitrite in nebulization form. Outstanding for the emergency relief of acute anginal pain. Each inhalation delivers precisely 0.25 mg. of octyl nitrite. By using the lungs as the most direct portal of entry, faster relief than from orally administered drugs is assured because of proximity of pulmonary and coronary circulations. Faster-acting than nitroglycerin. Fewer side effects than from nitroglycerin or amyl nitrite.

Only one or two inhalations necessary. One full minute should elapse between inhalations. In 10 cc. Medihaler bottle with metered-dose valve.

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LOS ANGELES

new improved formula!

"BEMOTINIC®" CAPSULES

In the treatment of all common anemias.

NOW 50% more Ferrous Sulfate
50% more Folic Acid
100% more Vitamin C

ALSO ADDED: ½ U.S.P. Unit of Vitamin B_{12} with intrinsic factor concentrate

THIS IMPROVED FORMULA CONFORMS TO THE MOST MODERN CONCEPT IN HEMATINIC THERAPY

"Bemotinic" Capsules

Each capsule contains:

Ferrous sulfate exsic. (4½ gr.)	300 mg.
Vitamin B_{12} with intrinsic factor concentrate U.S.P.	½ U.S.P. Unit
Vitamin C (ascorbic acid)	100 mg.
Folic acid U.S.P.	1 mg.
Thiamine mononitrate (B_1)	10 mg.

Supplied

No. 340—Bottles of 100 and 1,000.
Also available: "Bemotinic" Liquid No. 940—Bottles of 16 fluidounces and 1 gallon.

Dosages—Capsules

In microcytic hypochromic anemia: 1 or 2 capsules daily (preferably before or after meals), or as directed.
In macrocytic hyperchromic anemias: higher dosage levels necessary particularly in initial stages of therapy.

Ayerst **Ayerst Laboratories • New York, N. Y. • Montreal, Canada**

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fresh mixed

FOLBESYN*

VITAMINS LEDERLE

B+C

COMPLEX

assures full potency

Separate packaging of dry vitamins and diluent (mixed immediately before injection) assures the patient a more effective dose. May also be added to standard IV solutions.

Dosage: 2 cc. daily.

Each 2 cc. dose contains:

Thiamine HCl (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	50 mg.
Pyridoxine HCl (B_6)	5 mg.
Sodium Pantothenate	10 mg.
Ascorbic Acid (C)	300 mg.
Vitamin B_{12}	15 mcgm.
Folic Acid	3 mg.

Lederle

LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

when ACTH—

why ARMOUR'S

HP*ACTHAR® *Gel*?

because

HP*ACTHAR *Gel*
is the most widely used ACTH preparation—

HP*ACTHAR *Gel*
has the greatest volume of clinical experience—

HP*ACTHAR *Gel*
is regarded as the international standard of potency—

and

has a safety record unmatched by any other drug of comparable power, scope and action.

Some common indications from more than 100 diseases in which you can expect rapid effects from short-term therapy:

Allergies, including Asthma
Drug Sensitivities
Penicillin Reactions

HP*ACTHAR *Gel* is The Armour Laboratories Brand of Purified Repository Corticotropin (ACTH)

*Highly Purified

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY
KANKAKEE, ILLINOIS

Journal Report:

Hypertensive symptoms relieved in 96% of patients

"Comparison of pentolinium [ANSOLYSEN] with other preparations in 25 patients with severe essential hypertension, for whom all other methods of management had failed, showed that pentolinium is the most effective of available agents in reducing dangerously high blood pressure to the desired levels, and in modifying some of the complications of hypertension, as cardiac decompensation, cardiomegaly and retinopathy. . . .

"In 96 per cent (24 patients) clinical symptoms were relieved and the blood pressure maintained at comfortable levels. . . ."[1]

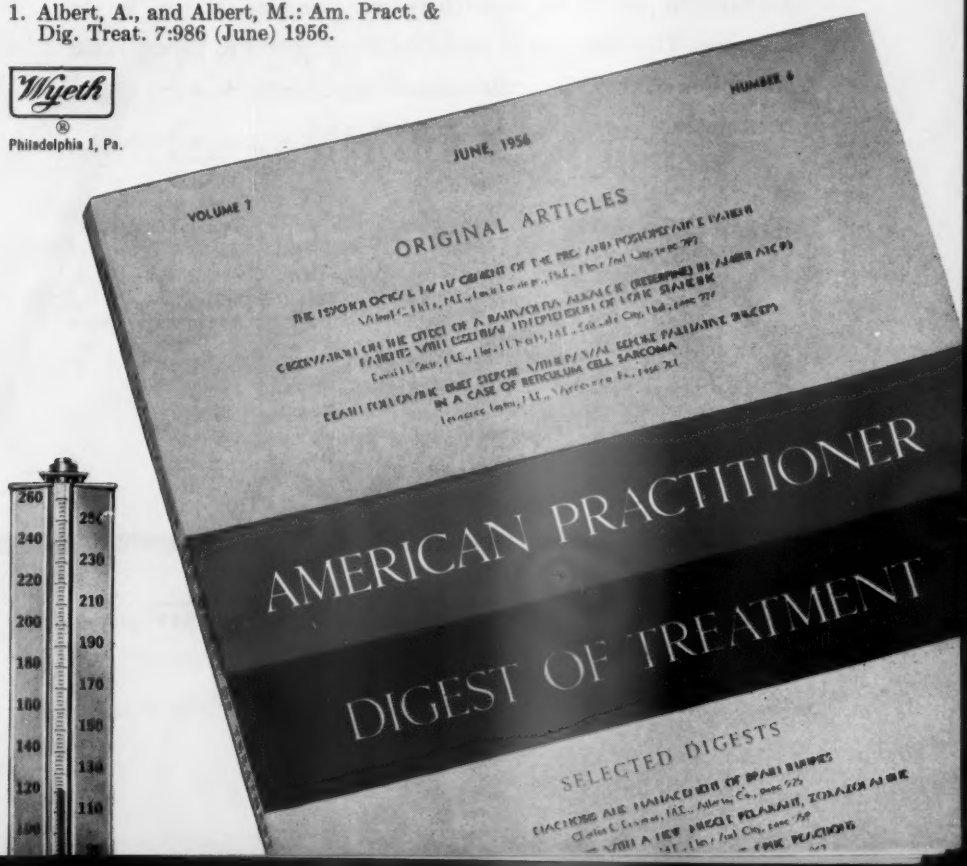
ANSOLYSEN®

TARTRATE — **Pentolinium Tartrate**

Lowers Blood Pressure

1. Albert, A., and Albert, M.: Am. Pract. & Dig. Treat. 7:986 (June) 1956.

Wyeth®
Philadelphia 1, Pa.



Now Buffered

for faster pain relief and superior gastric tolerance

A nonsystemic buffer (aluminum hydroxide) has now been added — in a new *"sequential release"* tablet — to the formulae of Pabirin and Pabirin AC (Pabirin plus hydrocortisone). The outer layer of this specially constructed and rapidly disintegrating tablet contains the aluminum hydroxide, PABA, and ascorbic acid. Within a few minutes the buffering action of the aluminum hydroxide is made available to protect the stomach against possible irritation by the salicylate. Then the core of the tablet disintegrates to permit rapid absorption of the other antirheumatic ingredients. As a result, gastric tolerance is excellent — pain relief rapid.



	Buffered Pabirin Tablets	Buffered Pabirin AC Tablets (Pabirin plus hydrocortisone)
Hydrocortisone		2.5 mg.
Acetylsalicylic acid (5 gr.)	300 mg.	300 mg.
Para-aminobenzoic acid (5 gr.)	300 mg.	300 mg.
Ascorbic acid	50 mg.	50 mg.
Dried aluminum hydroxide gel	100 mg.	100 mg.

Buffered Pabirin Tablets and Buffered Pabirin AC Tablets are DORSEY *preparations.*

potentiated salicylate therapy in "sequential release" form

for most rheumatoid arthritics

Buffered Pabirin Tablets represent the safest, fast-acting potentiated salicylate therapy which utilizes the synergism of PABA and acetylsalicylic acid to create *rapid, high* and *sustained* salicylate blood levels with *low* salicylate dosage.

BUFFERED
Pabirin®
TABLETS

Dosage: Average dose in arthritis, gout, arthralgia—two or three tablets 3 or 4 times daily. In rheumatic fever, three to five tablets 4 or 5 times daily.

Supplied: In bottles of 100 and 500 tablets.

for resistant rheumatics

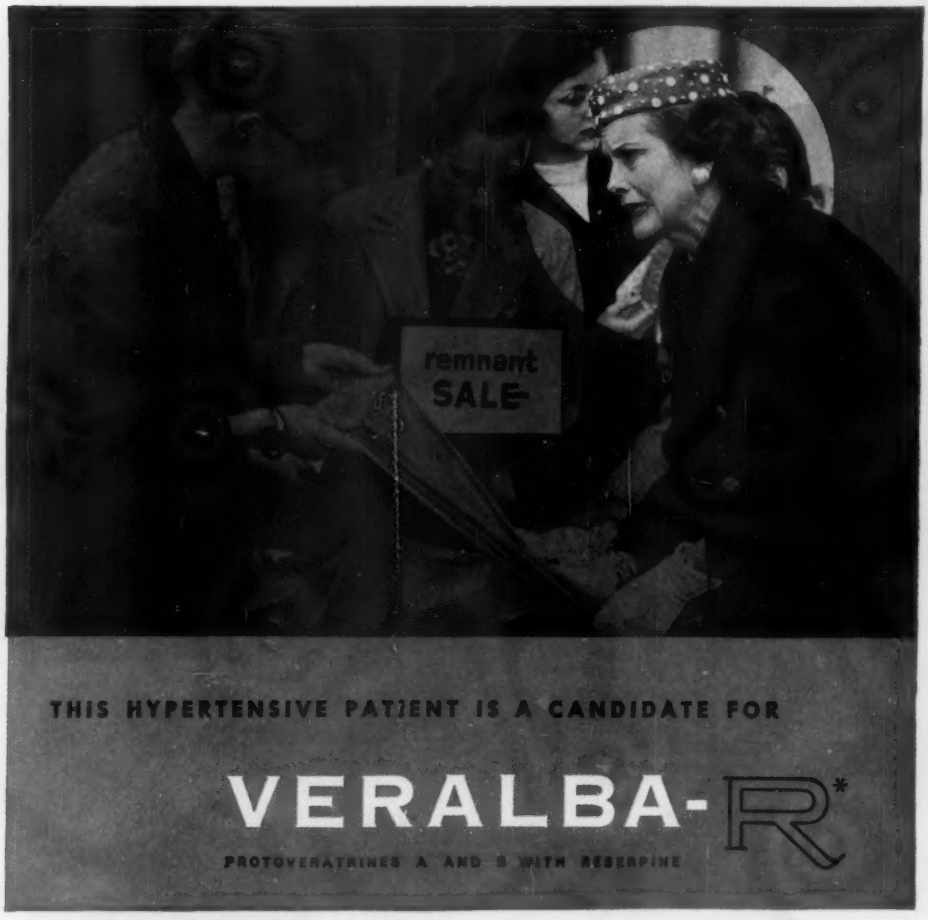
Buffered Pabirin AC (Pabirin plus hydrocortisone) Tablets. These new buffered tablets supply the extra steroid benefits of conservative amounts of hydrocortisone supplemented by the concurrent action of PABA, acetylsalicylic acid, and vitamin C. This combination creates high dosage steroid effects with low steroid dosage, thus minimizing the danger of adrenal atrophy.

BUFFERED
Pabirin® AC
PABIRIN PLUS HYDROCORTISONE
TABLETS

Dosage: Initially one or two tablets 4 times daily after meals and before retiring. Dosage should be reduced gradually.

Supplied: In bottles of 50 and 250 tablets.

SMITH-DORSEY • Lincoln, Nebraska • a division of The Wander Company



Conservative therapy in hypertension can be made more effective

EFFECTIVE: When combined with reserpine, hypotensive effects of protoveratrines A and B can be achieved with smaller dosage. Side effects are markedly reduced.

SAFE: Veralba-R can be given routinely without causing postural hypotension or impairing the blood supply to the heart, brain and other vital organs. Dosage is simple.

ACCURATE: Potency is defined by chemical assay. All ingredients are in purified, crystalline form.

Each Veralba-R tablet contains 0.4 mg. of protoveratrines and 0.08 mg. of reserpine. Bottles of 100 and 1000 scored tablets.

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PITMAN-MOORE COMPANY • *Division of Allied Laboratories, Inc.,* **INDIANAPOLIS 6, INDIANA**

NEW PRODUCT

ANNOUNCING



S.K.F.'s Duentric†-coated tablets make possible—
for the first time—

high, long-term dosage of **ASPIRIN**
without gastric upset

SKF

Indicated wherever high doses of aspirin are needed or wherever gastric discomfort makes therapy with ordinary aspirin tablets impractical—*particularly in rheumatic disease.*

Available: 'Ecotrin' ('Duentric'-coated) tablets, 5 gr., in bottles of 100.

Smith, Kline & French Laboratories, Philadelphia

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HOMAGENETS®*

better absorbed, better utilized

THE ADVANTAGES OF
HOMAGENETS

- Better absorbed, better utilized
- Excess vitamin dosage unnecessary
- Pleasant, candy-like flavor
- No regurgitation, no "fishy burp"
- May be chewed, swallowed or dissolved in the mouth

Homagenets provide, in tablet form, all the advantages of multi-vitamin drops. By a unique patented process, the vitamins are homogenized, then fused into a solid, highly palatable form. Homagenets supply vitamins in the same way as do the most nutritious foods.

Homogenization presents both oil and water soluble vitamins in microscopic particles. This permits greater dispersion of the vitamins—and consequently better absorption and better utilization.

*U.S. PAT. 2,676,136. OTHER PAT. PENDING

The S. E. MASSENGILL COMPANY • Bristol, Tennessee
New York • Kansas City • San Francisco

FOR MORE
DEPENDABLE
SULFONAMIDE
THERAPY

ALDIAZOL®-M

Aldiazol-M combines two of the most effective sulfonamides, sulfadiazine and sulfamerazine, with a systemic alkalizer, sodium citrate. High, prolonged blood levels are assured, while the danger of crystalluria is reduced.

Because of its inherent safety, it is often prudent to use Aldiazol-M instead of antibiotics and thus preclude the risk of sensitization.

Supplied as a suspension and as a tablet

Each teaspoonful contains:

Sulfadiazine*	0.25 Gm.
Sulfamerazine*	0.25 Gm.
Sodium Citrate	1.00 Gm.

Each tablet contains:

Sulfadiazine*	0.125 Gm.
Sulfamerazine*	0.125 Gm.
Sodium Citrate	0.250 Gm.

*Microcrystalline

The S. E. Massengill Company
Bristol, Tennessee
New York • Kansas City • San Francisco



Filmtab®

Nembu-Serpin®

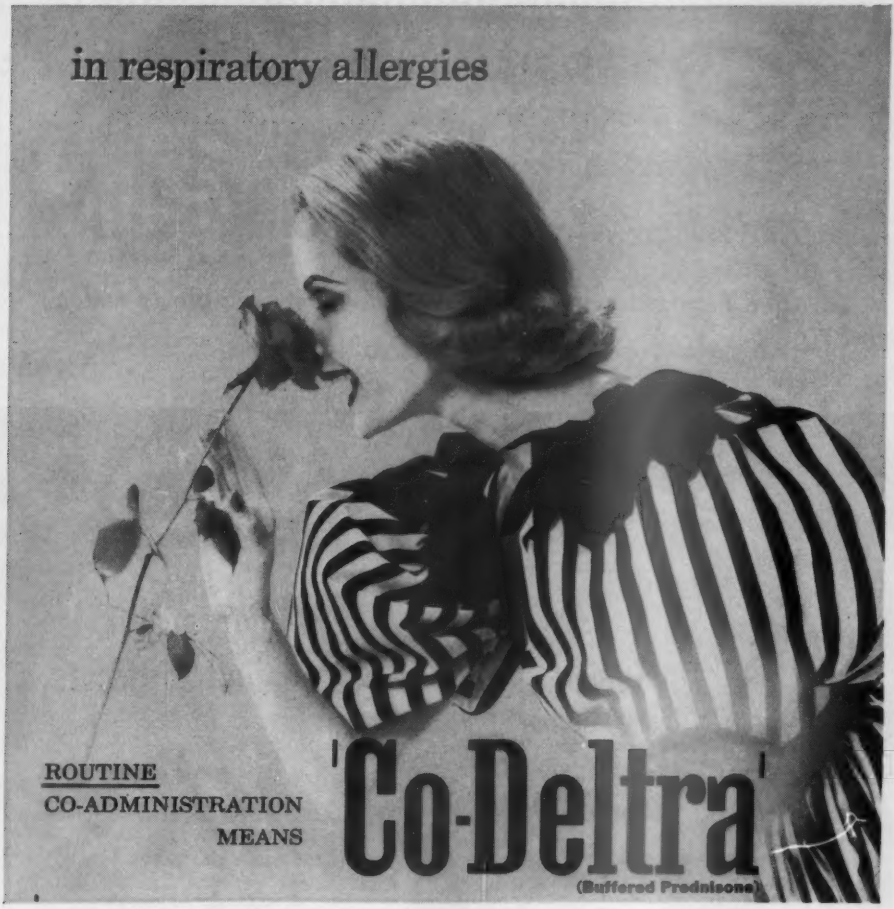
Restful nights are added to calm days for anxiety and mild hypertension patients when you prescribe Nembu-Serpin. The 30 mg. (½ gr.) of short-acting Nembutal (Pentobarbital Calcium) in each tiny Filmtab quickly induces drowsiness at bedtime, followed by refreshing sleep. Then the 0.25 mg. of longer-acting reserpine in each Filmtab calms patients all through the following days.

Patients experience almost immediate relief as Nembu-Serpin's sedative-tranquilizing action rapidly takes effect. Then their sense of well-being increases during the following few days. Nembu-Serpin avoids prolonged waiting for a cumulative response to reserpine.

Small dosages add safety, simplicity, economy for patients. Dosage schedules are simple, medication economical: just one Nembu-Serpin Filmtab at bedtime will calm the worries of most anxiety patients.
Nembu-Serpin Filmtabs—in bottles of 100 and 500. Abbott

® *Film-sealed tablets*
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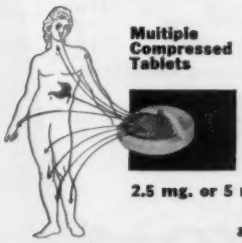
in respiratory allergies



ROUTINE
CO-ADMINISTRATION
MEANS

'Co-Deltra'
(Buffered Prednisone)

'Co-Hydeltra'
(Buffered Prednisolone)



Multiple Compressed Tablets

Clinical evidence[1, 2, 3] indicates that to augment the therapeutic advantages of prednisone and prednisolone, antacids should be *routinely* co-administered to minimize gastric distress.

2.5 mg. or 5 mg. prednisone or prednisolone with 50 mg. magnesium trisilicate and 300 mg. aluminum hydroxide gel.

SHARP & DOHME
Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

References: 1. Boland, E. W., *J.A.M.A.* 160:613, February 25, 1956. 2. Margolis, H. M., *et al.* *J.A.M.A.* 158:454, June 11, 1955. 3. Bollet, A. J., *et al.* *J.A.M.A.* 158:459, June 11, 1955.

'CO-DELTRA' *and* 'CO-HYDELTRA' *are the trademarks of* MERCK & CO., INC.

ALL THE BENEFITS OF THE "PREDNI-STEROIDS" PLUS POSITIVE ANTACID ACTION TO MINIMIZE GASTRIC DISTRESS

NOW...CORTICOID THERAPY OF SEVERE ASTHMA CAN BE MADE SAFER BY CONCURRENT THERAPY WITH Cardalin
(protected aminophylline)

Cardalin increases vital capacity...makes it possible to reduce dosage of corticoids and thus avoid risk of side effects

instead of these risks...

- activation and perforation of gastric ulcers
- water and salt retention
- nervous tension and undue mental stimulation

Cardalin

provides a full therapeutic dose of aminophylline orally without gastric irritation.

TO SERVE YOUR PATIENTS TODAY—
Call your pharmacist for any additional information you may need to help you prescribe Cardalin. He has been especially alerted.

these benefits with Cardalin + Corticoids

- safer control of asthma
- quicker remissions
- fewer side effects
- faster discontinuance of corticoids
- less costly treatment

Each tablet contains:

Aminophylline	5.0 gr.
Aluminum hydroxide	2.5 gr.
Ethyl aminobenzoate	0.5 gr.

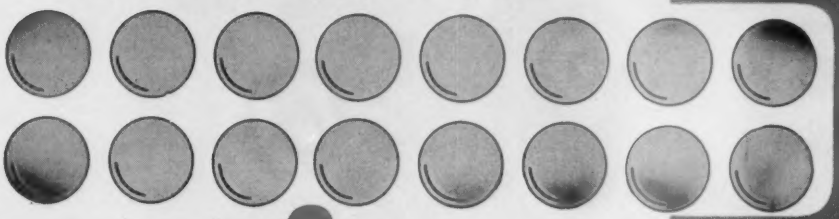
For Rx economy, prescribe Cardalin in 50's.

Also available—Cardalin-Phen, containing Cardalin plus ¼ gr. phenobarbital.

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

WHICH WOULD *YOUR* PATIENTS PREFER?

16 **ONE-HALF GRAM** ENTERIC-COATED
AMMONIUM CHLORIDE TABLETS



or only **8**

AMCHLOR

ONE GRAM ENTERIC-COATED
AMMONIUM CHLORIDE TABLETS *(Brewer)*



"Easy-to-swallow" AMCHLOR is processed in such a manner that each enteric-coated tablet contains 1 Gram of ammonium chloride and yet is not much larger than the 7½ gr. enteric-coated tablet. Thus the same dose can be given with only one-half the number of tablets.

FROM COAST TO COAST both physicians and patients are showing a decided preference for **AMCHLOR.**

SUPPLIED
bottles
of
100,
500
and
1000

The next time you prescribe ammonium chloride
specify—

AMCHLOR – Brewer

THE ONE GRAM enteric-coated tablet
of ammonium chloride
for your patients' convenience!

For samples just send your Rx blank marked — AMH

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BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.

prompt, prolonged relief for both



Peptic Ulcer *Hyperacidity*

Kolantyl

Kolantyl provides four beneficial actions that relieve pain and correct a range of gastric disorders characterized by spasm and low pH.

1. Acid neutralization; 2. Relief of spasm and hypermotility by musculotropic and neurotropic inhibition; 3. Inactivation of pepsin and lysozyme; 4. Formation of a protective demulcent.

Rx Information

Kolantyl

Gel and Tablets

Action:

Two-way spasmolysis . . . Spasm is relieved and gastric hypermotility is checked by the musculotropic and neurotropic effects of *Bentyl**—more effective than atropine, without the usual side effects.[1]

Rapid, Prolonged Antacid Effects[2] Balanced antacids act swiftly...do not cause laxation or constipation.

Demulcent Protection[3] . . . Normal tissue is safeguarded, and physiologic repair of damaged areas is enhanced.

Anti-enzyme Action[4] . . . Necrotic effects of pepsin and lysozyme are effectively curbed.

Composition:

Each 10 cc. (2 teaspoonfuls) of Kolantyl Gel or each Kolantyl Tablet contains:

Bentyl (dicyclomine) Hydrochloride	5 mg.
Aluminum Hydroxide Gel	400 mg.
Magnesium Oxide	200 mg.
Sodium Lauryl Sulfate	25 mg.
Methylcellulose	100 mg.

Dosage:

Gel—2 to 4 teaspoonfuls every three to four hours, or as needed.

Tablets—2 tablets (chewed for more rapid action) every three hours, or as needed.

Supplied:

Gel—12 oz. bottles. *Tablets*—bottles of 100 and 1,000.

*Merrell's distinctive antispasmodic that provides direct, fast relief of G. I. spasm and pain.

1. McHardy, G., and Browne, D.: South. M. J. 45:1139, 1952. 2. Hufford, A. R.: Rev. Gastroenterol. 18:588, 1951. 3. Johnston, R. L.: J. Indiana St. M. A. 46:869, 1953. 4. Miller, B. N.: J. South Carolina M. A. 48:245, 1952.

THE WM. S. MERRELL COMPANY
New York • CINCINNATI • St. Thomas, Ontario

Merrell
Since 1828

Pioneer in Medicine for Over 125 Years

TRADEMARKS: 'BENTYL', KOLANTYL®

relaxes both the body and the mind

well suited for prolonged therapy

- well tolerated, nonaddictive, essentially nontoxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to chlorpromazine or reserpine
- does not produce significant depression
- orally effective within 30 minutes for a period of 6 hours

Indications: **anxiety and tension states, muscle spasm.**

THE ORIGINAL MEPROBAMATE®

Miltown

Tranquilizer with muscle-relaxant action

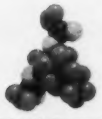
DISCOVERED AND INTRODUCED

BY WALLACE LABORATORIES, *New Brunswick, N.J.*

2-methyl-2-n-propyl-1,3-propanediol dicarbamate—U.S. Patent 2,724,720

SUPPLIED: *400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.*

Literature and Samples Available on Request



THE MILTOWN MOLECULE

CM-3668

reports of clinical studies

1 "I have used meprobamate in my general psychiatric practice since April, 1955, and believe it to be [a] drug of choice for relief of tension, anxiety and insomnia."

Lemere, F.: Northwest Med. **54**: *1098, 1955.*

2 ". . . the patient [taking Miltown] never describes himself as feeling detached or 'insulated' by the drug. He remains . . . in control of his faculties, both mental and physical, and his responsiveness to other persons is characteristically improved."

Sokoloff, O.J.: A.M.A. Arch. Dermat. In press.

3 "Of special importance is the fact that Miltown does not appear to affect autonomic balance—which in alcoholics is often unstable . . ."

Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. **17**: *19, 1956.*

4 "The [relative] absence of toxicity, both subjectively and objectively, is an important feature in favor of Miltown. In addition, there were no withdrawal phenomena noted on cessation of therapy, whether it was withdrawn rapidly or slowly."

Borrus, J.C.: J.A.M.A. **157**: *1596, 1955.*

5 "Miltown is of most value in the so-called anxiety neurosis syndrome, especially when the primary symptom is tension . . . Miltown is an effective dormifacient and appears to have . . . advantages over the conventional sedatives except in psychotic patients. It relaxes the patient for natural sleep rather than forcing sleep."

Selling, L.S.: J.A.M.A. **157**: *1594, 1955.*

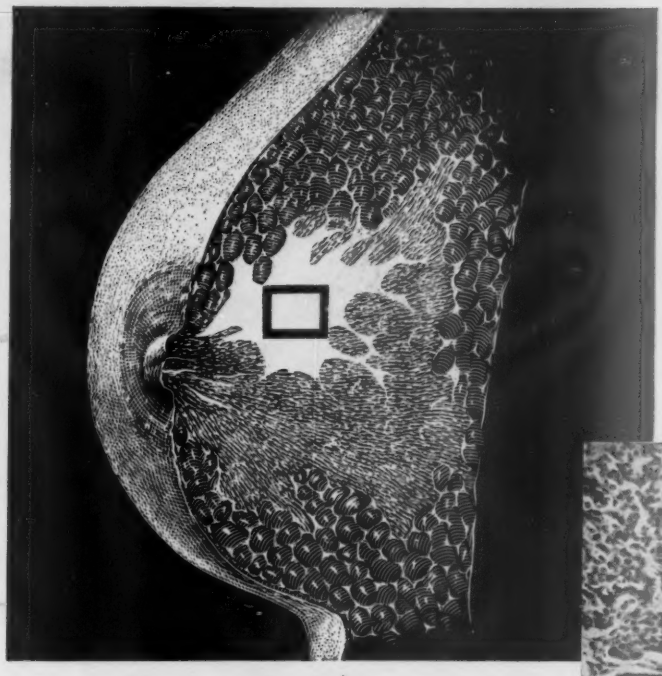
Miltown®

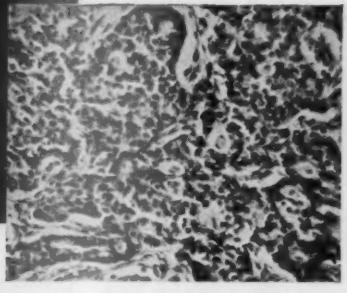
THE ORIGINAL MEPROBAMATE

discovered and introduced

by Wallace Laboratories, *New Brunswick, N.J.*

in **breast carcinoma...**
palliation smoothly maintained
with **Perandren**® phenylacetate





Androgens — in large doses — can provide palliation in advanced inoperable mammary cancer. Of all clinically used androgens, Perandren phenylacetate provides longer and stronger anabolic and androgenic effects — which are easily obtained, smoothly maintained.

One dose is usually effective for a full month

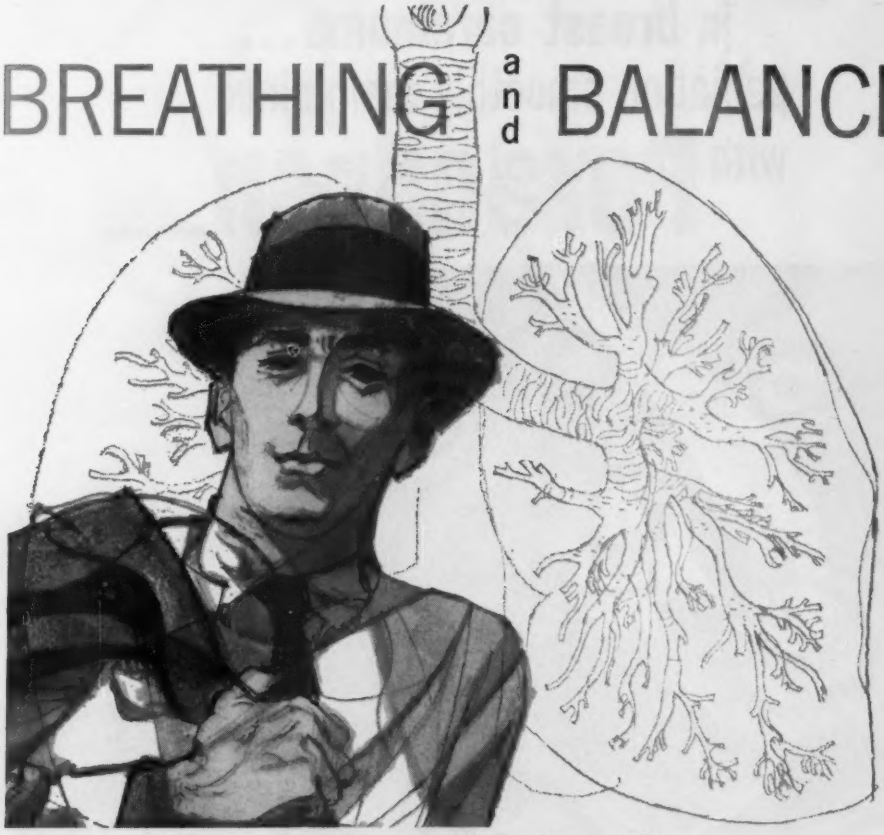
The virtually painless injection of Perandren phenylacetate spares the cancer patient much discomfort, frequency of injections, inconvenience.

Treatment should be started with short-acting Perandren *propionate* — 150 to 300 mg. *weekly*. When optimal dosage has been determined, the same amount of Perandren *phenylacetate* can then be injected — *once a month.*

Perandren® phenylacetate (testosterone phenylacetate CIBA): Multiple-dose Vials, 10 ml., each ml. containing 50 mg. Perandren phenylacetate. Perandren® propionate (testosterone propionate U.S.P. CIBA): Ampuls, 1 ml., each containing 25 mg. Perandren propionate; Multiple-dose Vials, 10 ml., each ml. containing 25, 50 or 100 mg. Perandren propionate.

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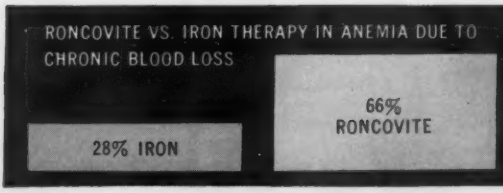
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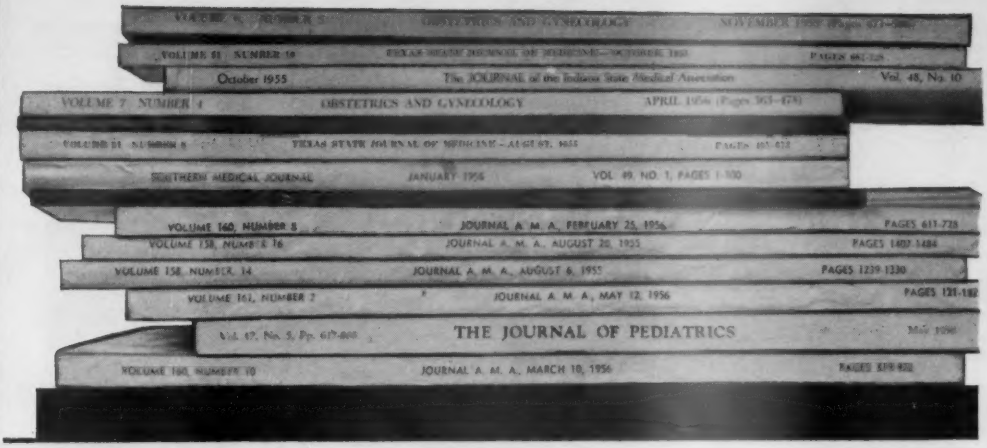
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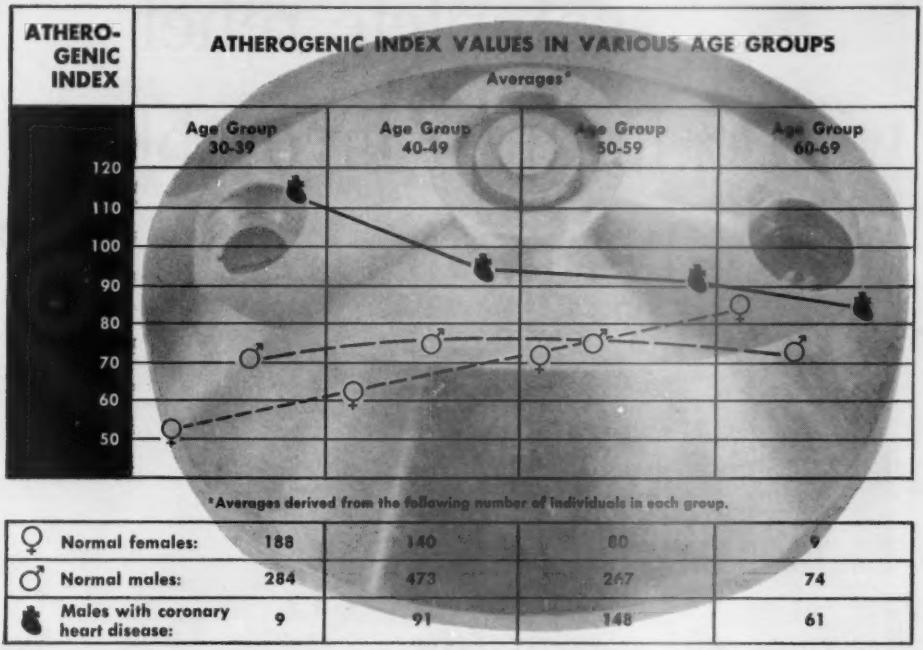
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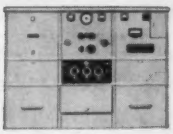
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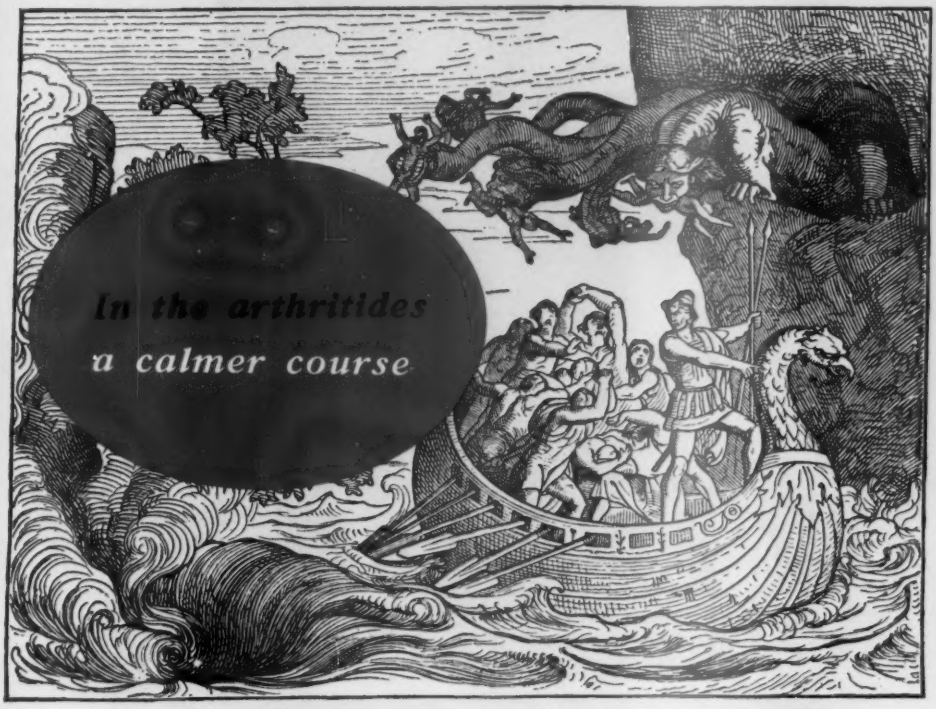
Contraindications: To be used with caution in patients with peptic ulcer, mental depression, cardiac conditions and related disorders.

Literature and Samples on Request

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[1] *Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med.* 11:*1105*

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References: 1. Gamble, J.R., et al. Arch. Int. Med. 95:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. 42:805, 1953.

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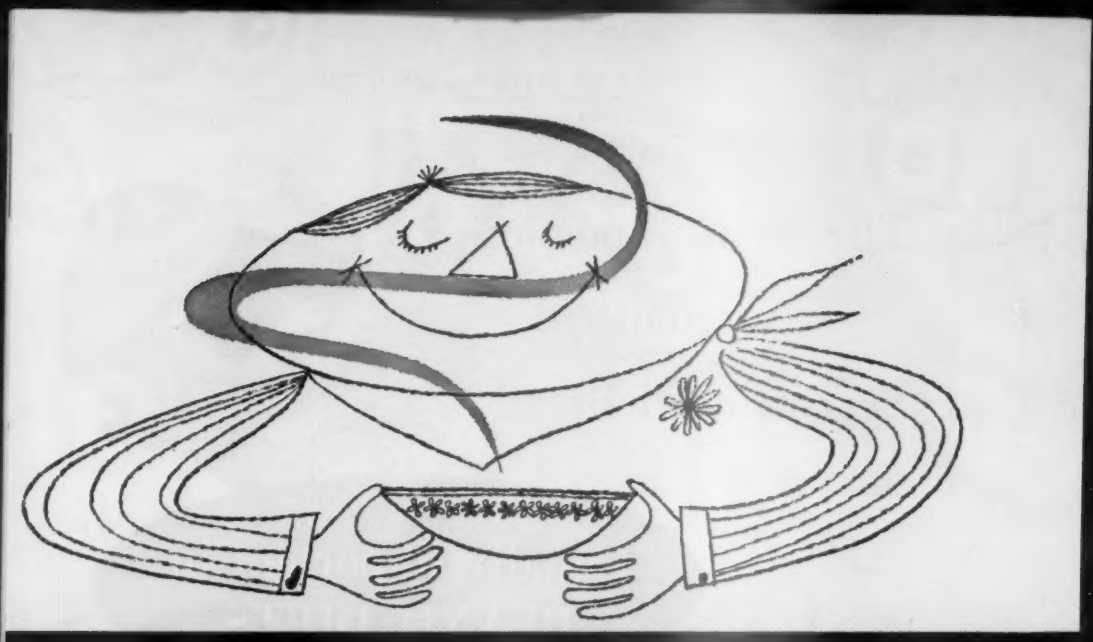
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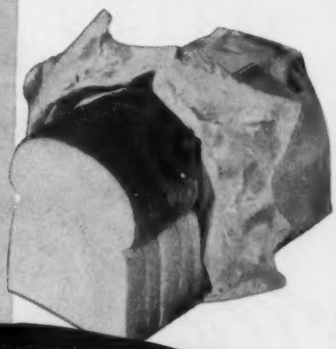
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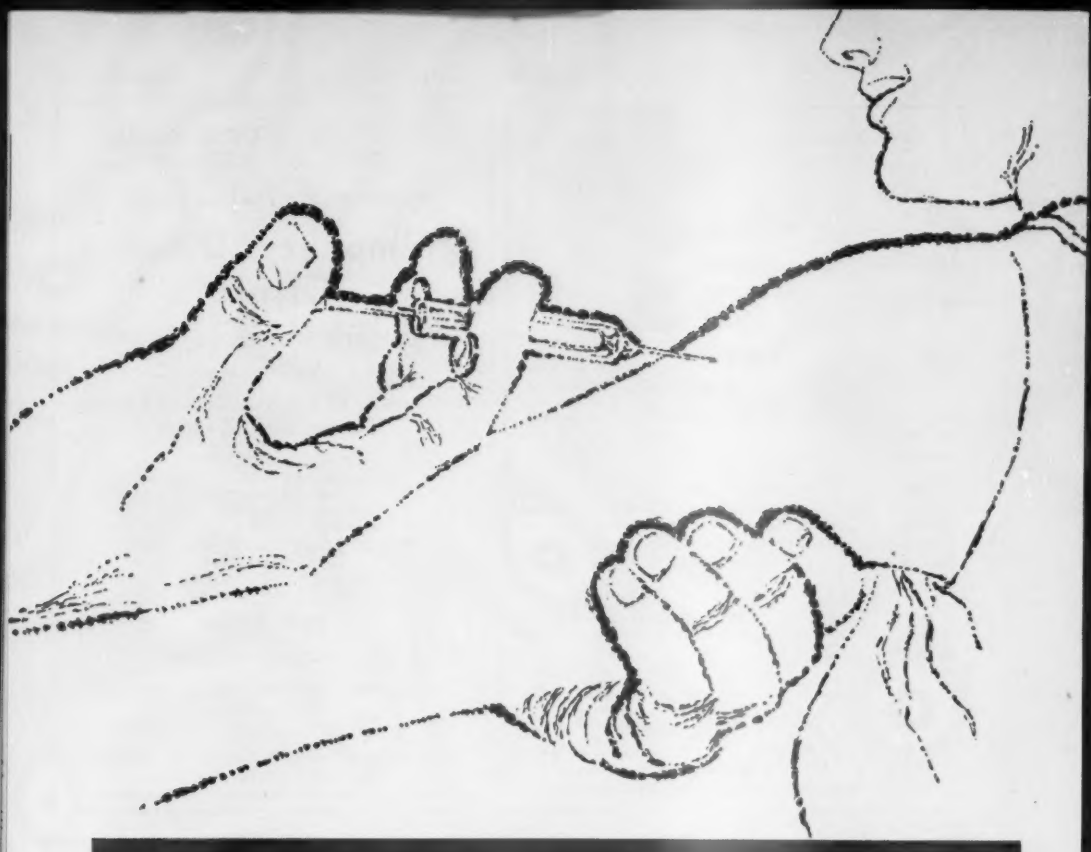
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1. New and Nonofficial Remedies. J.B. Lippincott Co., Philadelphia, 1956, p. 328. 2. Osol, A., and Farrar, G.E., Jr.: The Dispensatory of the United States of America. J.B. Lippincott Co., Philadelphia, 1956, pp. 808-809.

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1. Hardin, J. H.; Levy, J. S., and Seager, L. South. M. J. 47:1190, 1954.

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1. Binder, M. J., et al.: **Am. Jour. Med.**, 18:622, Apr., 1955. 2. Sampson, J. J., and Zipser, Albert: **Circulation**, 9:38, Jan., 1954. 3. Nichol, E. S., in Conn, H. F.: Current Therapy 1954. Philadelphia, W. B. Saunders Co., 1954, p. 196. 4. Jamison, W. L., et al.: **Jour. Am. Geriat. Soc.**, 3:521, Aug., 1955. 5. Gilchrist, A. Rae: **Brit. Med. Jour.**, 2:351, Aug. 16, 1952.

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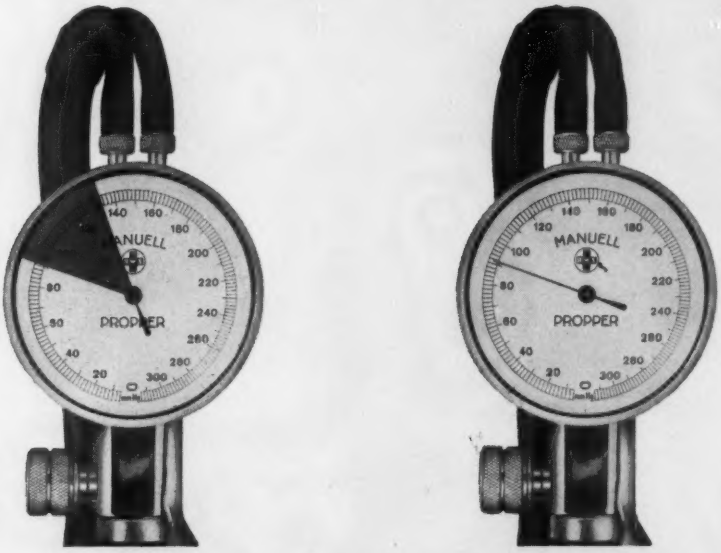
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Supplied: In bottles of 100, 500 and 1,000 tablets.

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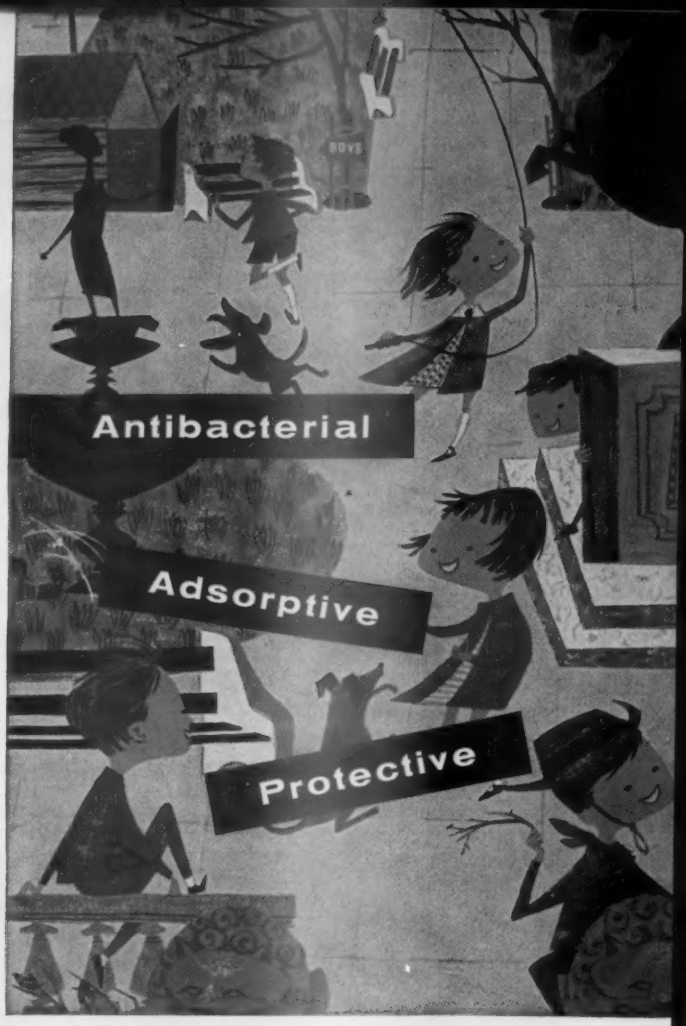
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2. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, The Macmillan Company, 1955, p. 754.

*Alseroxylon is that extract of Rauwolfia serpentina which contains a *complex* of hypotensive and tranquillizing alkaloids freed from the undesirable yohimbine-like alkaloids and the inert material of the whole root.

RAUVERA® RAUWOLFIA PLUS VERATRUM

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In diarrhea consider these clinical constants . . .



A potent specific in susceptible infectious diarrheas, STREPTOMAGMA provides *all* these actions. In 387 pediatric patients suffering from bacterial diarrheas, it was ". . . noticeable, most definitely, that STREPTOMAGMA stops the diarrhea sooner, more effectively, and with less recurrence."[1] For routine management in other forms of diarrhea, prescribe KALPEC®—pectin with kaolin in alumina gel.

1. Russ, J.D.: Personal communication.

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Dihydrostreptomycin Sulfate and Pectin with Kaolin in Alumina Gel

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- Hypertension associated with capillary fault induces a mortality rate 815% higher than that found in normotensives.[1] Quercetin can reduce this excessive rate by as much as 76%.[1]
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Each Capsule contains:

Choline bitartrate	349 mg.
Inositol (anhydrous)	167 mg.
dl-Methionine	84 mg.
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Quercetin	15 mg.
Ascorbic Acid	12.5 mg.
Vitamin B_{12}	2 mcg.

Supplied in bottles of 100 and 1000 capsules.
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VASCUTUM IS THE REGISTERED TRADEMARK OF SCHENLEY LABORATORIES, INC., FOR ITS LIPOTROPIC-ASTRINGENT-HEMOSTATIC PRODUCT. 30955

(1) Griffith, J. Q., Jr., et al.: Rutin and Related Flavonoids, Mack Publ. Co., Easton, Pa., 1955. (2) Griffith, J. Q., Jr.: Med. Clin. North America, November, 1954, p. 1717.

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in acute and chronic pyelonephritis, cystitis and prostatitis

freedom

from pain, infection and resistant mutants

"Frequently, patients reported symptomatic improvement within 24 hours."[1] Furadantin "may be unique as a wide-spectrum antimicrobial that . . . does not invoke resistant mutants."[2]

Comparative Sensitivity to Furadantin of Infectious Microorganisms Isolated over a Two-Year Period[3]

Microorganism	Total no. strains	Sensitive*		Moderately sensitive*		Resistant*	
		No.	Per cent of total	No.	Per cent of total	No.	Per cent of total
Proteus vulgaris	237	209	88.2	28	11.8	0	0
Escherichia coli (including paracolon bacillus)	281	255	92.7	23	8.2	3	1.1
Aerobacter aerogenes	223	183	82.1	40	17.9	0	0
Streptococcus faecalis	160	155	96.7	5	3.1	0	0
Pseudomonas aeruginosa	101	5	5.0	40	39.9	56	55.4
Micrococcus pyogenes var. aureus	6	6	100	0	0	0	0
Klebsiella pneumoniae	3	3	100	0	0	0	0
Alcaligenes faecalis	2	2	100	0	0	0	0

*Organisms inhibited by 100 μg./ml. or less are classified as sensitive, by 200 to 400 μg./ml. as moderately sensitive, and those not inhibited by 400 μg./ml. as resistant.

"The status of P. vulgaris and of M. pyogenes var. aureus is especially noteworthy in the light of the high degree of resistance exhibited by those organisms to antibiotics currently employed."[3]

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Furadantin®

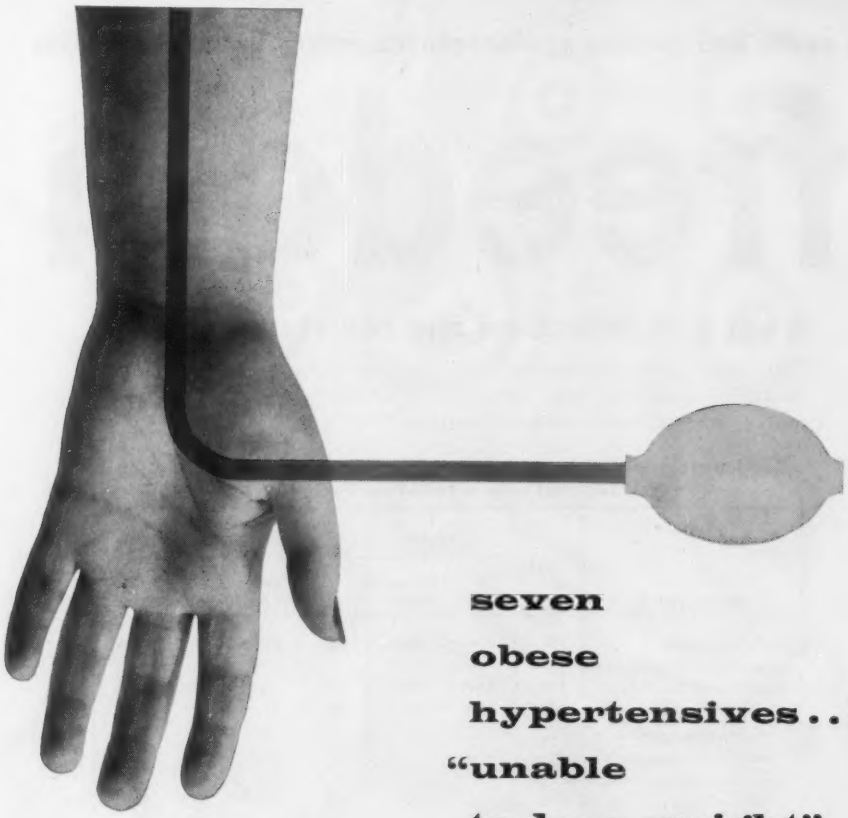
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FURADANTIN DOSAGE: Average adult dose is 100 mg., q.i.d. (at mealtime, and on retiring, with food or milk). Average daily dosage for children is 5 to 7 mg./Kg. in four divided doses.

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SUPPLIED: Tablets, 50 and 100 mg., bottles of 25 and 100. Oral Suspension, 5 mg., per cc., bottle of 118 cc.

NITROFURANS—a new class of antimicrobials—neither antibiotics nor sulfonamides



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obese
hypertensives...
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When treated with 'Dexamyl', all lost weight—an average of 25 pounds—and "the blood pressure was reduced . . . in all cases but one, in which there was no change."[1]

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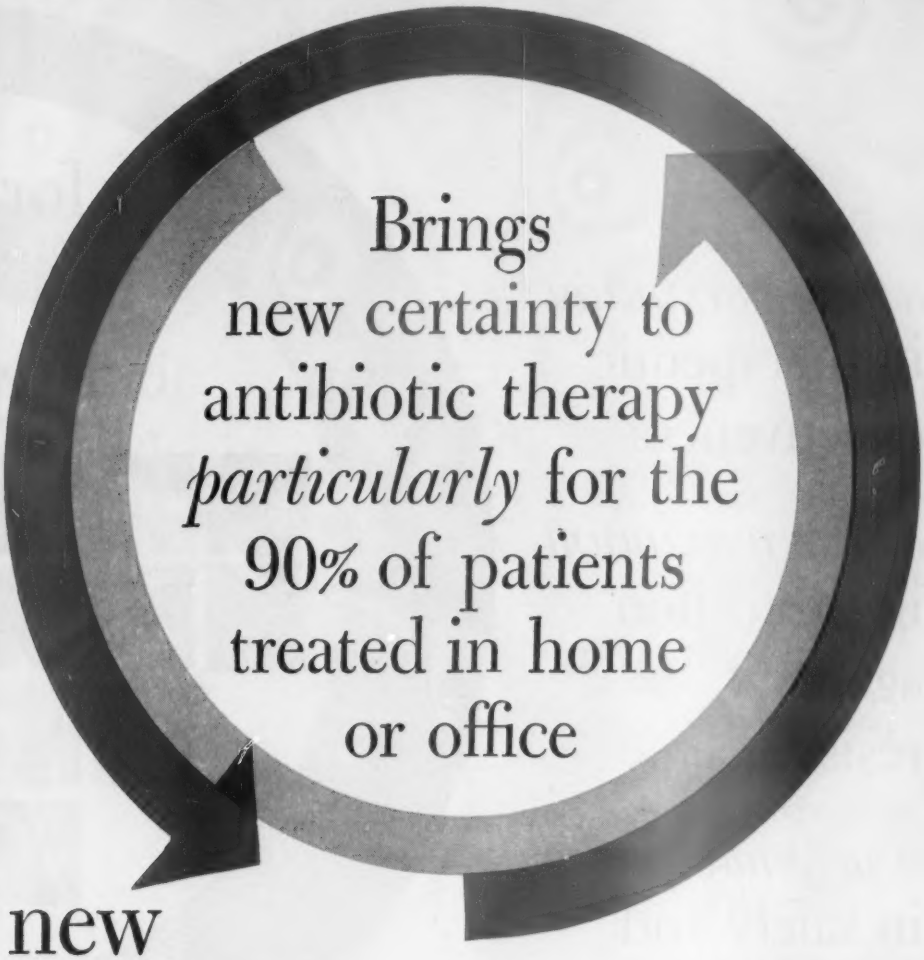
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Smooth **and** ***subtle*** **relief of the emotional factors that cause overeating and overweight**

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1. Roberts, E.: The Treatment of Obesity with an Anorexigenic Drug, Ann. Int. Med. *34*:1324.

*T.M. Reg. U.S. Pat. Off.
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Sigmamycin*

OLEANDOMYCIN TETRACYCLINE

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a new maximum
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multi-spectrum
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a new certainty
in antibiotic therapy,
particularly for
the 90% of patients
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Superior control of infectious diseases through superior control of the changing microbial population is now available in a new formulation of tetracycline, outstanding broad-spectrum antibiotic, with oleandomycin, Pfizer-discovered new antimicrobial agent which controls resistant strains. The synergistic combination now brings to antibiotic therapy: (1) a new fuller antimicrobial spectrum which includes even "resistant" staphylococci; (2) new superior protection against emergence of new resistant strains; (3) new superior safety and toleration.

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superior control of infectious disease through superior control of the changing microbial population

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A synergistically strengthened multi-spectrum antibiotic

Sigmamycin is a new antibiotic formulation providing: (1) the unsurpassed broad-spectrum activity of tetracycline, the outstanding broad-spectrum antibiotic discovered and identified by Pfizer; (2) the action of oleandomycin, the new antimicrobial agent which combats those strains, particularly among staphylococci, now resistant to tetracycline and other antibiotics.

Sigmamycin embodies a new concept in the use of antibiotics, for with this new synergistically active preparation, the development of refractory pathogens and their emergence as important sources of superinfection are more fully controlled.

New superior safety and toleration— Sigmamycin brings to antibiotic therapy new superior safety, new unexcelled toleration because: (1) tetracycline, an outstandingly well-tolerated antibiotic, is formulated with oleandomycin, also known to be remarkably free of adverse reactions; (2) the synergism between oleandomycin and tetracycline enhances antimicrobial potency.

Dosage: 1 to 2 capsules q.i.d.

Supplied: Capsules, 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.) Bottles of 16 and 100.

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Supplied: *Suspension*, bottles of 12 fluidounces. *Tablets*, bottles of 100. Samples sent promptly on request.

1. Kramer, P.: Med. Clin. North America, 39:1381, Sept. 1955.
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For Pain
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(Aspirin buffered with Maalox)
- Doubles blood salicylate level
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Because she is mentally "done in". Many of your patients—particularly housewives—are crushed under a load of dull, routine duties that leave them in a state of mental and emotional fatigue. For these patients, you may find 'Dexedrine' an ideal prescription. 'Dexedrine' will give them a feeling of energy and well-being, renewing their interest in life and living. Dexedrine* (dextro-amphetamine sulfate, S.K.F.) is available as tablets, elixir, and Spansule* capsules (sustained release capsules, S.K.F.) and is manufactured by Smith, Kline & French Laboratories, Philadelphia.

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Milligram for milligram,
Romilar is equal to codeine
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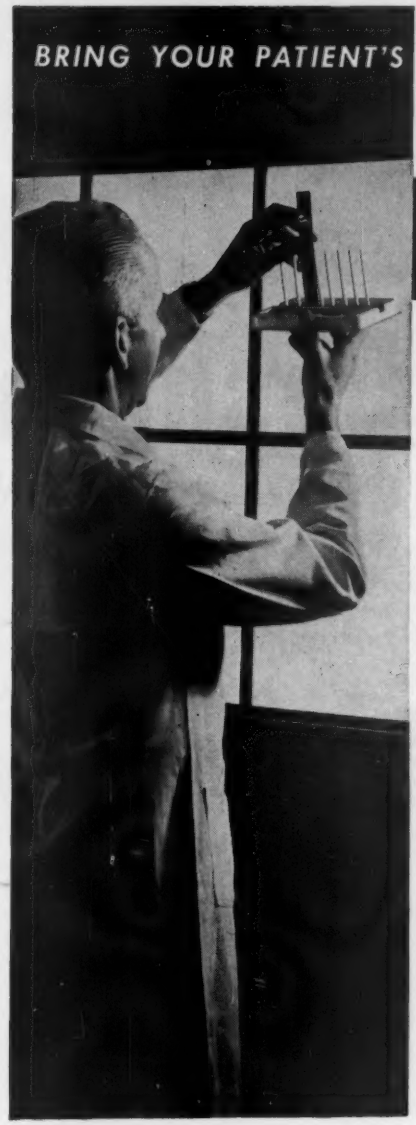
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Syrup, Tablets, Expectorant (w/NH_4Cl)



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- C-Reactive protein in serum only when inflammation exists.
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Both venous blood and blood obtained by the "finger tip technique" (punctured as for blood count) can be used with equally reliable results. To make the test procedure fast and convenient a new compact C.R.P.A. Test Kit is now available; it contains C.R.P.A., CRP-Positest control solution, capillary tubes, test rack, and illustrated directions.

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Tetracycline *Lederle*

for prophylaxis and treatment of

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Posner and his colleagues[1] have reported on the use of tetracycline (ACHROMYCIN) in 96 cases of obstetric complications, including unsterile delivery, premature rupture of the membranes, endometritis, parametritis, and other conditions. They conclude that this antibiotic is ideally suited for these uses.

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Every gram of ACHROMYCIN is made in Lederle's own laboratories and offered *only* under the Lederle label—your assurance of quality. It is available in a *complete* line of dosage forms, including

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ACHROMYCIN with STRESS FORMULA VITAMINS. Attacks the infection, bolsters the patient's natural defenses, thereby speeds recovery. Especially useful in severe or prolonged illness. Stress formula as suggested by the National Research Council.

SF Capsules, 250 mg.
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For more rapid and complete absorption. Offered only by Lederle!

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[1]Posner, A. C., *et al.*: Further Observations on the Use of Tetracycline Hydrochloride in Prophylaxis and Treatment of Obstetric Infections, *Antibiotics Annual* 1954-55, pp. 594-598.

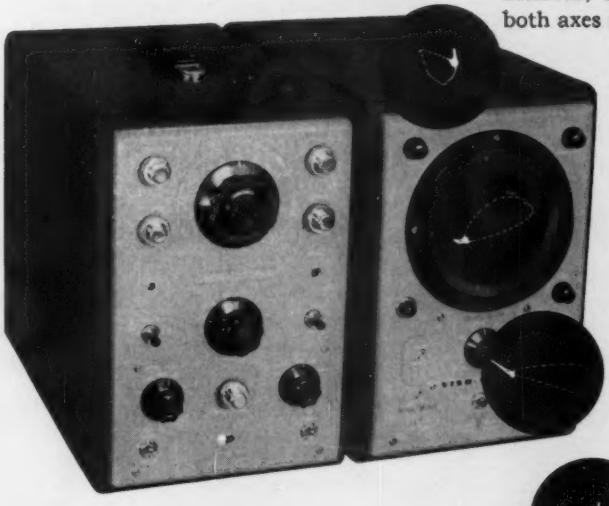
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FOR VIEWING EITHER VECTOR LOOPS OR REGULAR ECG LEADS



The SANBORN Vector Amplifier displays cube or tetrahedral vector leads — or ECG leads — on Viso-Scope screen

Specifically designed for use with the Sanborn Viso-Scope oscilloscope, this new Vector Amplifier provides complete and simplified control for all vectorcardiography functions. Any of 13 lead derivations are selected by turning a single knob. Other adjustments include control of trace width, height and position, frequency response and timing interval; selection of mirror images of both axes for photography; introduction of 1 mv standardization signal; beam intensity (Z axis) control.

In use, the vector loop or ECG complex appears as a sharply defined trace of long-persistence on the Viso-Scope screen. To photograph the image, a Fairchild, DuMont or other camera may be mounted on the Viso-Scope bezel.





BASIC FEATURES

Model 185 Vector Amplifier

LEADS

ECG: 1, 2, 3, AVR, AVL, AVF, V and STD position
TETRAHEDRON SYSTEM: Frontal, Sagittal and Horizontal
CUBE SYSTEM: Frontal, Sagittal, Horizontal
STD for simultaneous X and Y axis calibration for both tetrahedron and cube systems

SENSITIVITY: (Basic) 10″ per mv

PATIENT CONNECTION: 9 wire cable (4 tips marked for cube vectorcardiography) and 9 electrodes furnished

SIZE, WEIGHT: Compact case 13⅜″ x 9½″ x 19⅞″; weight 28 lbs.

Complete descriptive and operating data available on request.

The Model 179 Electronic Switch and Model 169A Viso-Scope are products of the same designers and makers as the well-known Viso-Cardiette, direct writing electrocardiograph.



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In Congestive Heart Failure
R_x 'Wide Safety Margin'
GITALIGIN®

WHITE'S BRAND OF AMORPHOUS GITALIN

Authoritative investigators have reported that the digitalizing dose of Gitaligin is approximately one-third the toxic dose.[1-5]

This "wide margin of safety" (difference between therapeutic and toxic doses) permits rapid digitalization and successful maintenance with a minimum of toxic side reactions—even in refractory cases where other glycosides have failed.[6] And, cost to your patient is no greater than ordinary digitalis preparations.

Supplied: Scored tablets of 0.5 mg. Bottles of 30 and 100.

References: 1. Ehrlich, J. C.: Arizona Med. *12:* 239 (June) 1955. 2. Weiss, A., and Steigmann, F.: Am. J. M. Sc. *227:* 188 (Feb.) 1954. 3. Dimitroff, S. P.; Griffith, G. C.; Thorner, M. C., and Walker, J.: Ann. Int. Med. *39:* 1189 (Dec.) 1953. 4. Heitmanek, M. R., and Herrmann, G. R.: Texas St. J. M. *51:* 238 (May) 1955. 5. Batterman, R. C.; DeOreff, A. C., and Rose, O. A.: Circulation *5:* 301 (Feb.) 1952. 6. Denham, R. M.: J. Kentucky St. M. Assoc. *53:* 209 (Mar.) 1955.

It's so easy to switch to 'wide safety margin' Gitaligin. Follow these simple dosage equivalents wherever digitalis therapy is indicated:

DIGITALIS PREPARATION	AVERAGE DAILY MAINTENANCE DOSE	GITALIGIN DOSAGE EQUIVALENT (APPROX.)
Digitalis leaf	0.1 Gm.	0.5 mg.
Digitoxin	0.1 mg.	0.5 mg.
Digoxin	0.5 mg.	0.5 mg.

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a new clinical study[1]

adds to the growing promise of

Sparine*

HYDROCHLORIDE

Promazine Hydrochloride

10-(γ-dimethylamino-n-propyl)-phenothiazine hydrochloride

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in a diversity

of common clinical conditions

1. Shea, J., et al.: Military Med. 119:221-227 (Oct.) 1956.

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● SPARINE Hydrochloride provides dramatic control of agitation in the acute psychotic, acute alcoholic, and drug addict. Especially promising has been the minimal toxicity observed—no case of liver damage has been reported.

In a new study, Shea and others[1] find SPARINE effective for control of a wide range of conditions associated with various medical emergencies. In a series of 47 cases the authors found:

"On all but 2 cases the doses used (25 to 200 mg.) permitted satisfactory control of such . . . problems as agitation, anxiety, nausea, vomiting, pain and hiccoughs."[1]

Clinical Report on . . .

PROMAZINE IN THE MANAGEMENT OF MEDICAL DISTURBANCES[1]

Case No.	Age	Diagnosis	Therapeutic Indication	Dose and Route	Duration of Therapy in Days	Response
1	56	Tetanus	Control convulsions and for relaxation	100 mg., q4h, I.V.	2	Good muscle relaxation Opisthotonos—no convulsions
2	36	Duodenal ulcer, D.T.'s	Control D.T.'s and nausea	50 mg., q6h, p.o.	6	No trouble with nausea
3	60	Peptic ulcer and hiatal hernia	For sedation	50 mg., q6h, p.o.	13	Good response—no pains
4	45	Pancreatitis—Gastritis	Hyperactivity	50 mg., q6h, p.o.	7	Good response—pain diminished
	42	Cirrh...	Hyper...	50 mg., q4h, I.M.	7	G...
7	40	Intracranial hemorrhage and M.S.	Pain in muscles	50 mg., q.i.d., p.o.	35	Good control of muscle pain
8	30	Ulcerative colitis	Pain from muscle and vomiting	100 mg., q6h, I.M.	36	Fair response
9	38	Sickle cell crisis Narcotic addict	Control pain	100 mg., q4h, p.o.	3	Good response
10	48	Rt. lower lobe pneumonia Chronic alcoholic	Control activity	100 mg., q6h, p.o.	12	Good response
11	44	Pneumonia	Vomiting and D.T.'s	50 mg., q6h, I.M.	6	Good response, immediate
			Abdominal pain		10	Good pain control
22	13	Uremia	Vomiting	25 mg., q6h	4	Vomiting controlled
23	57	Alcoholic (post)	D.T.'s and pain in chest	50 mg., q.i.d., I.M.	25	Controlled D.T.'s, pain relieved
24	42	Alcoholic (post)	Confused and disoriented	50 mg., q6h, p.o.	27	Fair control
25	71	HCVD—cerebral arteriosclerosis	Behavior problem	50 mg., t.i.d., p.o.	9	Good
26	47	Rheumatoid arthritis Acute excitation	Pain	50 mg., q6h, p.o. 50 mg., q6h, p.o.	3 5	Fair response
	16	Stricture of esophagus Pregnancy—hypertension	Vomiting	50 mg., q6h, I.M. 25 mg., q6h, I.M.	2 3	Controlled vomiting
		Chronic glomerulonephritis	Control nausea and vomiting	50 mg.	9	G...

In Constipation

NEW CONFIRMING

"...dioctyl sodium sulfosuccinate [Doxinate] results in restoration of normal function both in terms of stool consistency and frequency."

—CASS, L.J., AND FREDERIK, W.S.: AM. J. GASTROENTEROL. (DEC.) 1956.

"Our results indicate that effective fecal softening is generally adequate to permit correction of chronic constipation of the spastic type."

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PARTICULAR CONDITIONS FOR DOXINATE THERAPY

- Spastic Constipation
- Anorectal Conditions
- Pregnancy
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DOXINATE®

(DIOCTYL SODIUM SULFOSUCCINATE, **LLOYD**)

THE ORIGINAL FECAL SOFTENER

DOSAGE:

ADULTS—2 or 3 soft gelatin green 60 mg. capsules daily.

INFANTS—1 or 2 cc. Doxinate Solution 5% once daily in milk, formula or fruit juice.

CLINICAL RESEARCH

"In the atonic group,...the simultaneous use of mild laxation [Doxinate with Danthron]...is preferred...."

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DANTHRON

PATENT PENDING

IS FREQUENTLY PREFERRED IN:

- Atonic Constipation
- Chronic Functional Constipation
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Danthron (1,8-dihydroxyanthraquinone) is a mild, non-habit forming peristaltic stimulant acting only on the large bowel.

DOSAGE:

For adults and children over 12—one or two soft gelatin brown capsules (containing Doxinate, 60 mg.; Danthron, 50 mg.) at bedtime for 2 or 3 days or until bowel movements are satisfactory.

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"In the interest of medicine since 1870"

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ATARAXOID is a unique, new combination of STERANE and ATARAX, which now permits simultaneous symptomatic control and reduction of attendant anxiety and apprehension in rheumatoid arthritis and other indications.

The added tranquilizer control, desirably easing mental stress, also directly assists clinical progress. It minimizes the chance of exacerbation related to emotional strain and facilitates patient confidence and cooperation in the therapeutic program toward maximum rehabilitation.

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The ataractic effect is a central neuro-relaxing action — the result of a marked cerebral specificity — free of mental fogging and devoid of any major complications: no liver, blood or brain damage. This peace-of-mind component is also used in the lowest dosage range.

Supplied: Each green, scored, ATARAXOID oral tablet contains 5 mg. prednisolone (STERANE) and 10 mg. hydroxyzine hydrochloride (ATARAX). Bottles of 30 and 100.



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prednisolone and hydroxyzine

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combining the newest, safest tranquilizer, ATARAX® + the newest, most effective steroid, STERANE® (prednisolone)

simultaneously controls the symptoms and the apprehension

In Rheumatoid Arthritis, other collagen diseases, bronchial asthma and inflammatory dermatoses

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- reduces rigidity and tremor.
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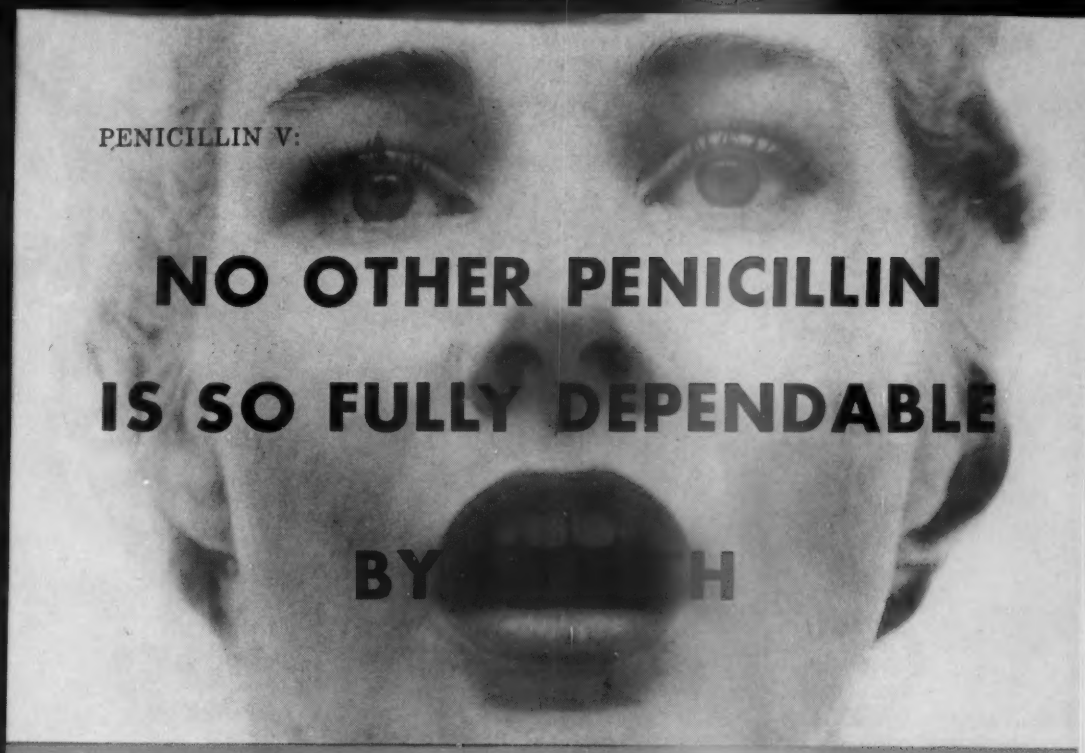
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1. Welch, H.: Antibiotic Med. *2*:11 (Jan.) 1956.

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CONGENITAL INDIFFERENCE TO PAIN *

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THE condition spoken of as "congenital indifference to pain" is a rarity often discovered by chance. In the case of a child, the parents may eventually realize that a long series of injuries and illnesses has occasioned none of the suffering which would ordinarily have been expected. The subjects of congenital indifference to pain—who are in no way mentally retarded, hysterical or psychotic—present no objective anomaly of sensation. They can detect, identify and localize pinpricks, and can distinguish quite minor differences in thermal contacts. Sometimes the subject is also insensitive as to smell and taste. Furthermore, itching often lies outside the subject's sensory experience. Neurologic examination yields no abnormality other than sluggish or absent corneal responses. Scars and arthropathies may bear witness to earlier painless traumata. Experimental interventions which might be expected to give rise to pain provoke neither a verbal protest nor mimic responses, such as wincing, nor yet any vegetative reflex activity.

Congenital indifference to pain is a specific entity which needs to be distinguished from the relative analgesia of the mentally retarded, the hysteric and the insane. It must also be differentiated from cases where there obviously is a chronic and extensive organic affection of the sensory pathways (e.g., lumbar syringomyelia, tabes, neuritis). At times (as perhaps in Biemond's case), congenital indifference to pain has been confused with the sensory radicular neuropathy (with or without deafness) of Hicks, Denny-Brown [1, 2] and others. Diagnostic difficulties are especially likely when the clinical problem is encountered in a very young subject. Congenital indifference to pain needs also to be separated from the condition described by Schilder and Stengel [3] under the term "pain-asymboly"; here,

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the syndrome is not innate but develops relatively late in life, after lesions typically located near the supramarginal gyrus of the dominant hemisphere.

Weir Mitchell [4] was probably the first to record a case of congenital indifference to pain. It concerned a legal friend of his who died at the age of 56 years. At no time in his life had he ever experienced pain keenly. Having had his finger crushed in the course of a political altercation, he bit it off. For three years a toe was the seat of a painless ulcer. A spreading abscess threatened his life: it evoked no pain whatsoever, and none was felt when it was lanced. An operation for the bilateral removal of cataracts was carried out without an anesthetic. Only on his deathbed did he complain of a little discomfort. Other similar cases, occurring in adults, were briefly described by Dearborn [5] * and by Critchley.[6, 7] Thereafter, attention was alerted and other cases were discovered, many of them in children. Ford and Wilkins [8] described three such cases, while Kunkle and Chapman [9] studied an adult example. Then followed a report by Boyd and Nie,[10] with a mention in the ensuing discussion by Grain [11] and von Hagen [12] of other cases. Arbuse, Cantor and Barenberg [13] briefly described an example, as did Roe.[14] McMurray's detailed study [15] is of particular value. Moffie's patient [16] was a complicated one. Jewesbury [17] published a paper dealing with four instances, one of which concerned a young child who was apparently outgrowing this indifference to pain. Farquhar and Sutton,[18] Girard, Devic and Garin [19] and Madonick [20] each described one case. In the discussion which followed the presentation of the last case, Parcella [21] referred to three similar examples and Ziegler [22] to one, all of whom had been patients at the New York Neurological Institute. Another recent case is the one recorded by Kipnis, Cohen, Kubzansky and Kunkle,[23] though it might be argued that some of the features were atypical in many important respects. The latest instance in the literature is the case recorded by Ortiz de Zarate.[24]

Clinical Discussion

There appear to be no significant factors demonstrable in the etiology. The syndrome has been identified at all ages but, not unnaturally, medical attention is first aroused comparatively early in life. Males and females are equally afflicted. A familial incidence seems to be exceptional, though Schilder [3] mentioned two siblings with this syndrome. Nielsen, according to von Hagen, observed the syndrome in two sisters. Many racial stocks have been identified, and one case at least has been described in a Negro.

* Dearborn's patient at one time appeared in vaudeville as "Edward H. Gibson, the human pincushion." In his act he would invite members of the audience to thrust pins into any part of him except the abdomen and groins. As many as 60 pins might be driven in up to their heads. A challenge of $5,000 was offered to any physician who could detect signs of pain. Once he prepared a crucifixion: a wooden cross was erected on the stage, with four gold-plated spikes with needle-sharp points ready for use. An assistant hammered one of the nails through the palm of the hand and he would have continued had not the performance been broken up at this juncture by the collapse of various members of the audience.

No special features can be traced in the ancestry. In some of the recorded cases one or both parents have been of subnormal intelligence. On the other hand, the parents of McMurray's [15] patient were of superior mental endowment. In some instances, ambidexterity or left-handedness has been explicitly mentioned in the subject with congenital indifference to pain.

The outstanding phenomenon consists in the patient's toleration of putative painful stimuli applied to cutaneous and mucous surfaces. This appears to justify the epithet of "universal" indifference to pain. As already stressed, no real hypalgesia exists, and, indeed, there may be little if any alteration in the threshold for any modality of sensation. But the indifference to pain may prove on scrutiny to be neither absolute nor universal. This statement deserves closer attention. Although in most cases there has been a lifelong immunity to the aches and pains of minor maladies—headache, colic, dysmenorrhea, neuralgia—exceptions may occur. Again, serious systemic or visceral disease may run a remarkably painless course in the majority of instances; but, here too, this may not always be so. Traumatic and experimental nocipotentive measures typically produce no suffering; but here again, anomalies may arise. The case records in the literature bear witness to these deviations:

"Patient could recall no pain except headache" (Dearborn [5]).

"Suffered from headache and colic in association with attacks of pyelitis" (Ford and Wilkins, case 3 [8]).

"Complained of being hurt after being struck on the hip by a stone. Moderate toothache once. Mild discomfort on very firm testicular pressure" (Kunkle and Chapman [9]).

"Disliked uncomfortably cold water and objects" (Boyd and Nie [10]).

"Itching from a skin rash. Unpleasant feeling after 5 minutes testicular compression" (Jewesbury, case 1 [17]).

"Recent feverish headaches. Experienced pain with acute appendicitis. Some slight pain after testicular compression maintained for 7 minutes. Later, developed mild migraine" (Jewesbury, case 2 [17]).

"Recalls a day's headache with vomiting in 76 years, and a painful episode of urinary retention" (Jewesbury, case 3 [17]).

"Has experienced abdominal discomfort" (Madonick [20]).

"A throbbing headache following a spinal anaesthetic" (Kipnis, Cohen, Kubzansky and Kunkle [23]).

In one or two instances the passage of time seemed to bring about some modification of the syndrome of indifference. This was most conspicuous in Jewesbury's fourth case,[17] which concerned a little boy of three and one-half who, during his first two and one-half years of life, had shown no reactions to injury. He was in the habit of chewing his fingers till they bled. Burns and other traumata evoked no protest. He handled stinging nettles with equanimity. When 22 months old he was written up in the Press as "the child who knows no pain." McMurray's patient [15] was a college graduate of 22 years who believed that her congenital indifference towards pain was tending somewhat to decrease. McMurray was not con-

vinced, however, and wondered whether a more restrained adult behavior was perhaps responsible. The first patient described by Ford and Wilkins [8] submitted to many potential ordeals while in hospital; latterly, he began to act as though afraid he would get hurt. He refused to have a carious tooth pulled without an anesthetic. It seemed as though the child was becoming more aware of pain and more sensitive to it.

Comparatively few of the patients have been investigated as thoroughly as modern neurology would ordain. The patients written up by McMurray,[15] by Jewesbury,[17] by Kunkle and Chapman,[9] and by Kipnis, Cohen, Kubzansky and Kunkle [23] are therefore important. Their results can be tabulated:

Histamine Injection:

1. Vasodilatation and a sense of throbbing, but no headache (McMurray [15]).
2. Flushing, but no headache (Kunkle and Chapman [9]).
3. Flushing, subjective warmth; no headache (Jewesbury, 1 [17]).
4. Flushing and feelings of warmth; no headache (Jewesbury, 2 [17]).
5. Throbbing, but no pain (Kipnis et al.[23]).
6. No headache (Madonick [20]).

Muscle Ischemia:

1. Tight feeling after five minutes, but no pain (Jewesbury, 1 [17]).
2. After five minutes, no discomfort (Jewesbury, 2 [17]).
3. After seven minutes, no pain or discomfort (Jewesbury, 3 [17]).
4. No pain . . . (Kunkle and Chapman [9]).
5. No pain . . . (McMurray [15]).
6. After four minutes, only a light feeling . . . (Kipnis et al.[23]).
7. No pain . . . (Madonick [20]).

Electric Shock:

1. Patient did not object to faradic stimulation of 4 ma (while control subjects withdrew sharply with 2 ma for 1 millisecond) (Jewesbury, 1 [17]).
2. Subject did not object to a faradic current of 40 ma applied for 1 or 200 milliseconds (Jewesbury, 2 [17]).
3. No pain from electric shocks (McMurray [15]).

Ciliospinal Reflex:

1. Negative (Arbuse et al.[18]).
2. Negative (Ford and Wilkins [8]).
3. Negative (McMurray [15]).
4. Negative (Kipnis et al.[23]).
5. Present (Kunkle and Chapman [9]).

Psychogalvanic Responses:

1. Nil (Ford and Wilkins, 2 [8]).
2. Nil from limbs, feeble response from the face (Ford and Wilkins, 3 [8]).

Cold Pressor Test:

1. Somewhat increased (?) (Kunkle and Chapman [9]).
2. Normal (Arbuse et al.[13]).
3. Negative (McMurray [15]).
4. Negative (Madonick [20]).
5. Intact (Kipnis et al.[23]).

A few remarks upon the question of terminology are worth while. Authors have spoken more or less interchangeably of "congenital indifference to pain" and "congenital insensitivity to pain." Of these alternatives, the former is preferable. Not only does it describe what actually appears to be the process at work, but it also avoids the ambiguity of the term "sensitivity" which might unwittingly suggest some loss of pain-feeling.

The term "congenital" has also been replaced by the adjective "constitutional" at the hands of some writers. Others, again, have introduced the word "universal" in speaking of congenital (or constitutional) indifference to pain. This, we submit, is misleading at times, and at other times is unnecessary. Grain's [14] patient, it is true, did not show a universal distribution of areas from which putative painful stimuli evoked no protest. Thus, contacts over the tip of the nose, the corneae, the pharynx and the skin of the neck produced a normal reaction of discomfort and displeasure. But Grain's patient was not fully documented, and in any event, the case seems to be atypical in some of its features. To speak of "analgesia" or "natural analgesia" in connection with this syndrome is of course not warranted.

Discussion

The real problem concerns the nature and fundamental basis of the syndrome of congenital indifference to pain. Up to now, discussion as to pathogenesis has of necessity been speculative. No autopsy study of a case has yet been made. Even were such an opportunity to present itself, it does not by any means follow that the problem would be solved, or even materially simplified.

Discussion has largely resolved itself into two main questions: Are we dealing with some inborn anatomic anomaly of the pain pathways somewhere in their extent, or are we concerned with a disorder of function in the widest sense of the word? If the latter notion is favored, the further question arises as to whether a psychogenic disorder is envisaged.

Skin biopsies have been carried out at times and have yielded a perfectly normal picture of nerve-endings and neurofibrils. (There is a doubtful

exception to this statement in the case reported by Ortiz de Zarate.[24]) This normal finding supports the contention that there is no inborn defect of the pain-pathways at a peripheral level, as had been mooted by Gasser at one time.

That there might be a structural anomaly at a thalamic level has been suggested from time to time, e.g., by Grain.[11] Something resembling an agenesis or congenital maldevelopment has been envisaged, involving certain thalamic nuclei. This idea has not been supported by the appearance of the ventriculogram in those few instances where air studies have been carried out. Neither, for that matter, does the clinical picture suggest a thalamic type of disorder of pain-experience.

Many writers have drawn analogies with the attitude toward pain which lobotomized patients so often display. This has in turn led to the conception of some defect located at the highest level, and in particular within the frontothalamic connections.[12]

In most of the cases where clinicophysiologic methods of investigation have been utilized, the results seem to have pointed to a relatively high-level defect. Thus the local axon reflexes have proved to be intact in all cases available for quotation. True, the responses to the cold pressor test have varied, but the behavior of the psychogalvanic reactions certainly indicates a lesion at a high level, at the same time excluding a picture of hysterical analgesia. The case studied by Kipnis et al.[23] is an exception, however. Largely because of the prolonged anesthesia following the application and subsequent release of a constricting cuff, the authors visualized a comparatively inferior type of sensory defect. Whether their arguments are adequate must remain open, but in any event the case studied must be deemed not quite typical of the syndrome of congenital indifference to pain, if only because of the altered threshold to pain and temperature in their case.

The most remarkable feature in this syndrome is a typical lack of conformity between the feeling of pain as a discriminative quality of sensation, and the registration of distress, either overtly or automatically. Thus we have a dissociation between the various components of a normal pain-experience, i.e., (1) the qualifying notion of pressure, cutting, heat, etc., which constitutes the nature of the pain; (2) the highly unpleasant sensation which constitutes the specific sense-datum of pain, and (3) the feeling-tone of displeasure. The first component is cognitive in nature, while the second and third are affective. In cases of congenital indifference to pain the first component is intact, while the third is in abeyance, and perhaps also the second. This discrepancy is reminiscent of what may follow the operation of lobotomy, and also the pain asymboly of Schilder and Stengel;[3] it differs from these conditions, however, in that they also entail a defect of the second component, i.e., the specific pain-feeling. This component may or may not be intact in cases of congenital indifference to pain.

Other terminologies are sometimes used in this connection. Ford and

Wilkins [8] spoke of two factors within a normal response to a noxious stimulus, viz., (1) a crude sensation of pain, and (2) an affective reaction to the pain. They believed that it is the second factor which is lacking in cases of congenital indifference to pain. Hardy, Wolff and Goodell (1943) spoke of three factors: (1) the sensation of pain; (2) the "dolorous effect," or recognition of the sensation as being sharp or painful; and (3) aversion, with reactionary movements of avoidance or protection.

For reasons such as these, a highest level defect is generally favored. A congenital type of pain asymboly is sometimes envisaged, possibly associated with a parietal aplasia. The term "agnosia for pain" has been used by some and disapproved of by others, who have preferred to hypothecate an inherent disturbance in the emotional capacity to react to pain.[12] The underlying notion is, however, not very different. The coexistence in some cases of high-grade mental defect, of unstable cerebral dominance or of epileptic tendencies has led to the suspicion that a focal or diffuse cerebral agenesis may be responsible. But in other cases, again, the subject has been one of normal intelligence, and even above average in some instances. This fact had led to an analogy with such allegedly specific disabilities as congenital word-blindness, "congenital auditory imperception" and congenital aphasia. Unfortunately, the uncertain status of these innate disorders of language does not encourage one to trace comparisons with the syndrome of indifference to pain.

Yet another line of argument avoids the invocation of structural lesions within the neuraxis. In normal individuals there is unquestionably a sort of spectrum of pain-experience which extends from those relatively tolerant of uncomfortable somatic sensations, to the other end of the scale occupied by the "sensitives." Whether these extremes represent differences in the intensity of the crude feelings of pain, or only in the feeling-tone of displeasure, or of both, is uncertain. Expressed differently, it is debatable whether the scale comprises a difference in cognitive or in affective factors, or a combination of the two.

Can it be that the victims of congenital indifference to pain represent those otherwise normal persons who happen to lie at one extremity of this spectrum—being offset by those who are constitutional hypersensitives? This idea would be rather supported by observations such as that of Nielsen, who is said to have known three sisters, two of them victims of congenital indifference to pain, the third being unusually intolerant toward pain. The hypothesis is also perhaps supported by the two well established and important clinical points, namely, the *occasional* experience of visceral or superficial pain, and the tendency for subjects to lose some of their hyposensitivity later in life.

To look upon these cases as occupying one end of a natural scale or gamut of sensitivity does not necessarily entail any morphologic defect. An analogy with congenital word-blindness or with Daltonism may be less

apposite than with, say, the possession of a "musical ear" or the faculty of absolute pitch.

Perhaps the weightiest argument against this "natural" hypothesis is the extreme nature of the indifference towards pain. In ordinary experience, the scale of natural variation in sensitivity would seem to be a rather restricted one. Whether this argument is sufficient to upset the hypothesis must, for the time being, remain open.

Within the domain of visceral pain we may perhaps see much more individual variation in sensitivity than in the case of superficial pain. Thus, cardiologists have long been intrigued by the examples of cardiac infarction occurring without any trace of pain. Common experience teaches that many otherwise ordinary and unexceptional persons are immune from headache, notwithstanding perhaps a long experience of head injury, overindulgence, febrile maladies and the like. Such phenomena are inexplicable, and it is interesting to note that victims of congenital indifference to pain may also exhibit painless coronary thrombosis,[17] and be more or less ignorant of headache.

That subjects with congenital indifference to pain experience some perverted somatic sensations, particularly in the very young, is rather suggested by the common habit of gnawing the fingers and chewing the tongue. Such practices might be an effort to assuage or to alter an unpleasant dysesthesia. Or, they might be indulged in as a deliberate means of provoking a pleasurable but unnatural experience. Thus, Boyd and Nie's [10] patient, a girl of seven, would pick her nose till the nostrils became ulcerated, saying that "it tickled." Often she burned herself on a hot stove because ". . . it felt good." The small child demonstrated by Roe [14] seemed to be merely amused when potentially painful stimuli were applied.

Obviously not enough cases have yet been seen, or studied well enough, to justify firm conclusions as to pathogenesis. Time will doubtless rectify this defect. In the first place, we ought to know far more about the natural history of these cases, particularly of those of early age. A follow-up study is sorely needed of such cases as the three children originally described in 1938 by Ford and Wilkins.[8] Do such persons tend gradually to lose their tolerance towards pain, and do they in due course undergo painful experiences? The records of McMurray [15] and even of Kipnis et al.[23] rather suggest that the syndrome can continue into early adult life, while the original observations made by Critchley,[6, 7] by Dearborn [5] and by Weir Mitchell [4]—however inadequate as to details—suggest that the indifference to pain may persist in middle age. Are such cases the exception or the rule?

We need to know more about the status of other forms of discomfort in these cases. In some of the recorded examples, hunger and thirst have not been conspicuous—indeed, probably nonexistent. Toleration of distended bladder has also been described. Unusual endurance of climatic

extremes has been noted. Defective olfactory and gustatory sensibility has been recorded, but there have been no alterations reported in visual or auditory acuity. Painless menstrual periods are on record, but we have no knowledge of a subject of congenital indifference to pain becoming pregnant. Is childbirth painless in such women? More data are needed.

Few observers have gone into the question of whether congenital indifference to pain entails also an anhedonia, or indifference to pleasurable somatic experiences. Deficiencies in the realm of smell and taste lead one to suspect that this may be the case at times. But information is sadly lacking. "Tickle" is said to be intact in some of the very young subjects, but the sense of "itching" is usually lost. Itching, however, is scarcely a straightforwardly pleasurable experience, being rather an attenuation of pain, or a "slow pain" as Rothman puts it. We know nothing of the integrity or otherwise of libidinous or erotic feelings, though we may recall that masturbation has been practiced by at least one child with congenital indifference to pain. Whether pleasure can be achieved by dint of environments of cosy warmth or coolness, or by caressing or soothing touches, or by the muscular activity achieved by exercise or dancing, is still unknown.

More information is needed as to whether the threshold for the appreciation of sense-data really is unaltered. Kunkle's [9] application of the Hardy-Wolff-Goodell technic leads to a certain doubt, in some cases at least. We would also welcome more study on the pattern of recovery of function after muscle-ischemia, an argument which has been taken as favoring a low-level lesion. Perhaps, as Denny-Brown [2] tentatively suggested, there may be more than one type of congenital indifference to pain.

Much more knowledge is wanted as to the psychologic aspects of these cases of congenital indifference to pain, especially in later life. The alleged biologic importance of pain has been exaggerated, it is granted, but it is inconceivable that a lifelong immunity from pain can fail to influence the emotional life of the subject. While it has been specifically stated that abnormal states of indifference toward the sufferings of others, with possible sadomasochistic trends, do not occur, it may well be that minor traces of this kind may develop. A glance at the case records of the children with this syndrome reveals quite clearly that unusual emotional or behavioral pictures of one kind or another are the rule. Mention has also been made of the curiously "flat" language-behavior of some of the older subjects, indicating perhaps a certain poverty of sensorial experience.

The clinical neurologist's identification of this curious syndrome offers, then, considerable scope, both for investigation and for thought. Congenital indifference to pain is a very worthy subject for the attention of the neurophysiologist, but the returns may well prove to be richer and still more rewarding to the psychologist, and also to the philosopher.

SUMMARIO IN INTERLINGUA

Le syndrome de un congenite o constitutional indifferentia a dolor es un rar entitate specific que debe esser distinguite ab le analgesia relative de retardamento mental, hysteria, e follia. Illo etiam debe esser differentiate ab casos in que il existe un obvie affection chronic e extense del vias sensori, i.e. per exemplo syringomyelia, tabes, neuritis, e neuropathia radicular sensori. Finalmente, illo debe esser distinguite ab casos del si-appellate "asymbolia de dolor."

Individuos con le ver syndrome de indifferentia constitutional a dolor manifesta nulle objective anomalia de sensation. Illes es capace a deteger, identificar, e localisar piccaturas de agulia, e illes pote distinguer satis parve differentias thermic. In certe casos le individuo es etiam insensibile a odores e gustos, e a vices ille ha nunquam experientiate prurito. Le examine neurologic revela nulle anormalitate, excepte pauco active o absente responsas corneal. Cicatrices e arthropathias pote testificar le previe occurrentia de traumas sin dolor. Interventiones experimental que deberea causar dolor evoca ni protestos verbal ni responsas mimic ni reflexos vegetative.

Nos ha non ancora un clar comprension del natura fundamental de iste syndrome. Per exemplo, on non sape ancora si il existe in iste casos un innate anomalia del vias de dolor o si le disordine es simplemente un disordine "functional" in le plus comprehensive senso del termino. Ab le puncto de vista physiologic on pote asserer que le defecto se trova a un relativemente alte nivello, e le analogia del comportamento de patientes lobotomisate es frequentemente signalate.

Le aspecto typic del condition es que illo ignora omne conformitate inter le sensation de dolor (incluse le discrimination qualitative de grados de dolor) e le registration de molestia, de maniera que on pote parlar de un dissociation inter le componentes cognitive e affective del normal experientia de dolor.

Il es possibile que iste syndrome representa solmente un extremo in un hypothetic "spectro de sensibilitate a dolores" in le population normal.

Es signalate le analogia del casos de normal individuos qui pare esser insensibile a certe catastrophes e affectiones visceral—per exemplo le casos de non-dolorose infarcimento cardiac—e del casos de personas qui ha nunquam experientiate mal de capite.

Individuos con congenite indifferentia a dolores interpreta possibilemente le putativemente dolorose stimulos que illes recipe como stimulos de character agradabile.

Il es non ancora cognoscite si individuos con congenite indifferentia a dolores cognosce o non cognosce le experientia de sensationes somatic de character placente.

Iste problema representa ancora un vaste campo de opportunitate pro futur investigationes e cogitationes. Illo merita le attention del neurologo clinic, del psychologo, e del philosopho.

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THE CURRENT PROBLEM OF STAPHYLOCOCCAL INFECTIONS *

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During the last decade staphylococcal infections have become a problem of increasing concern. Most of the acute bacterial infections of man respond promptly and predictably to the antimicrobial agents now available. Nevertheless, infections due to staphylococci have remained a serious therapeutic problem. It is generally believed that the incidence of staphylococcal infection has increased since the introduction of antimicrobials, although only a few studies to document this impression have appeared in the literature.[9, 42, 64]

Despite the apparent close biologic relationship between staphylococci and other gram-positive cocci which produce acute human infections, there is increasing evidence to suggest that staphylococci may differ from these microörganisms in fundamental humoral-cellular relationships within the animal or human host. Certain biologic properties of staphylococci may have a bearing on the pathogenicity and chronicity of staphylococcal infections. By the same token, recent experimental studies suggest that certain host mechanisms, or changes in host resistance, may serve to perpetuate staphylococcal infection, or to convert the staphylococcal carrier state into active disease.

The clinical situations in which serious staphylococcal infections arise in 1956 differ in many important aspects from the clinical syndromes noted during the pre-antimicrobial period. There is abundant evidence to indicate that antimicrobial therapy has not been successful in dealing with a number of the serious staphylococcal infections seen in hospitalized patients today.

It is the purpose of the present paper to examine certain aspects of the staphylococcus-host relationship which may have bearing on the current therapeutic problem, and to review our experience in the management of staphylococcal infections.

Biologic Characteristics of Staphylococci Which May Relate to Pathogenicity

The adaptability of staphylococci is relatively unique among the microorganisms commonly producing disease in man. In contrast to most micro-

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bial species, pathogenic *Staphylococcus aureus* strains have broader in vitro biochemical characteristics than their nonpathogenic *Staphylococcus albus* brethren. Strains of staphylococci which cause infection in man generally produce pigment, ferment a wide variety of sugars, and elaborate extracellular toxin and a number of enzymes and hemolysins. In in vitro situations they can adapt to the most unfavorable of nutritional circumstances, rapidly acquiring the ability to synthesize their own amino acids from simple nitrogen-containing salts.[36] There is some evidence to suggest that strains of staphylococci are more heterogeneous than many other pathogenic microorganisms, each culture possessing individual mutants which may allow survival under a wide variety of circumstances.

Staphylocoagulase: The majority of staphylococci isolated from human infections elaborate an extracellular enzyme, coagulase, which possesses the ability to clot the plasma of certain animal species.[35, 51, 54, 80] It has been shown that the conversion of fibrinogen to fibrin requires the presence of a serum factor reacting with coagulase to form a thrombin-like substance.[80, 90] Recent work by Tager suggests that the serum coagulase-reacting factor may be prothrombin or smaller molecules derived from prothrombin.[89]

The possession of this unique enzyme system, and the high correlation between coagulase production and virulence, have led to much work designed to determine the rôle of coagulase in the initiation and establishment of staphylococcal infections. Hale and Smith have suggested that coagulase serves to protect staphylococci at the site of infection by the creation of a protective fibrin envelope about clumps of microörganisms, thus preventing their phagocytosis.[38] While it is clear that the presence of a coagulable menstruum does decrease the ingestion of coagulase-positive staphylococci in vitro, studies by Rogers and Tompsett indicate that staphylococci are nevertheless avidly phagocyted in the presence of fibrin, under circumstances in which other microörganisms are rarely ingested.[71] Ekstedt has recently suggested that coagulase serves to protect pathogenic staphylococci from certain serum components inhibiting staphylococcal growth.[23, 24] Whether these studies indicate protection from an actual bacteriostatic factor present in serum, or merely reflect the ability of coagulase-positive strains to multiply in less attractive biologic situations because of their broader adaptability, remains to be determined.

Certain animals which lack a coagulable plasma appear resistant to local abscess formation when injected with coagulase-producing strains of staphylococci. Nevertheless, localized infection can be produced in these animals when a coagulable plasma is simultaneously injected.[81] Rammelkamp has shown that staphylococcal abscess formation is rare in birds who do not possess coagulase-reacting factor, and has noted that infants with staphylococcal infections tend to develop diffuse inflammatory lesions rather than the focal abscesses characteristic of infection in the adult.[66] His data, graphically represented in figure 1, indicate that children under two gen-

erally possess considerably lower serum titers of coagulase-reacting factor than adults.

Thus these observations suggest that coagulase may operate to localize staphylococcal disease, producing chronic foci from which relapse may ensue. Nevertheless, studies by other investigators indicate that local abscess formation occurs during the course of experimental infections in mice, despite the absence of a coagulable plasma in this animal.[52, 57, 77] Recent experiments

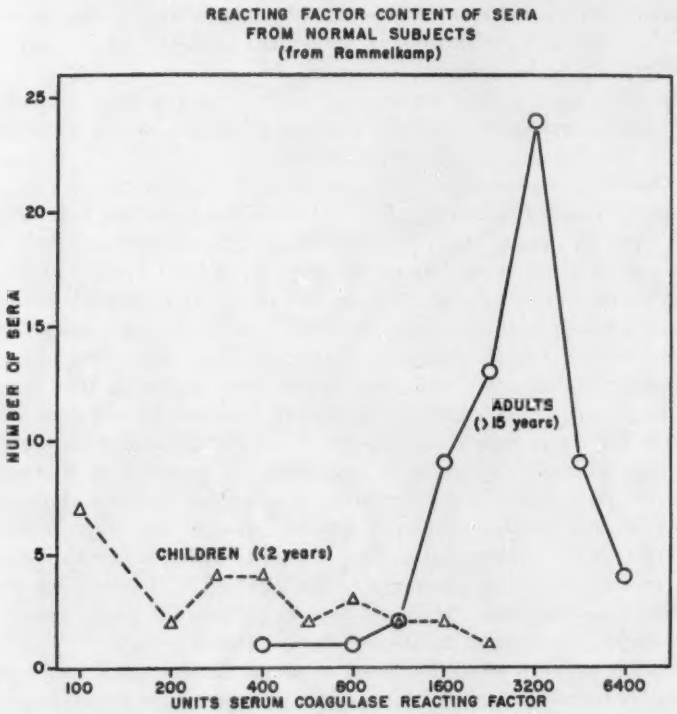


FIG. 1. The coagulase-reacting factor content of sera obtained from normal children and adults (after Rammelkamp[66]).

by Smith and Dubos demonstrated that different strains of staphylococci show a spectrum of virulence in the mouse which correlates well with the ability of these strains to produce coagulase, but the rôle of coagulase per se in the initiation or maintenance of such mouse infections remains uncertain.[77]

Coagulase has been demonstrated to be antigenic for animals and man.[65, 66, 88] Boake has recently shown that rabbits immunized against coagulase survive for longer periods than unimmunized control animals following intravenous challenge with coagulase-positive staphylococci.[10] Neverthe-

less, such immunized animals die of disseminated infection, with multiple renal abscesses indistinguishable from the lesions observed in control rabbits.

Despite the high correlation between coagulase production and human virulence of staphylococcal strains, many studies have been unable to assign coagulase a convincing rôle in the establishment or perpetuation of staphylococcal infections.[25, 30, 71, 77] It thus seems possible that coagulase is merely another index of the broad array of biologic properties which characterize virulent strains of staphylococci, and that the actual factor or factors responsible for virulence may merely occur in association with coagulase production.

Extracellular Toxin: Many coagulase-positive staphylococci produce a potent exotoxin which causes severe dermal necrosis in animals and man.[62, 83, 92] It appears unlikely, however, that exotoxin production plays a rôle in the initiation of human infection. In a recent study on human volunteers, Elek was unable to demonstrate a relationship between toxin production and the number of staphylococci necessary to produce a cutaneous abscess.[25] In certain instances of established human staphylococcal infection, the clinical picture of fulminating illness, with high fever, cyanosis, vomiting, diarrhea, tachycardia and the rapid development of shock, mimics the syndrome produced in animals by the injection of exotoxin.[48, 76, 83] The Bundaberg disaster, in which 21 children were inoculated with diphtheria toxin-antitoxin contaminated with staphylococcal exotoxin, produced a similar syndrome.[46] Nevertheless, immunization of experimental animals with exotoxin does not protect against death due to staphylococcal infection, merely converting acute fulminating disease to a more chronic form characterized by renal abscess formation and, later, death.[48]

Other Extracellular Enzymes: A number of other extracellular enzymes have been shown to be elaborated by staphylococci in vitro. Leukocidin, an enzyme destroying leukocytes in vitro,[62, 92] various hemolysins[26] and hyaluronidase[72] are produced by certain strains of staphylococci. The rôle of these substances in the initiation or maintenance of staphylococcal infections has not been clarified.

Host Responses Which May Perpetuate Staphylococcal Infections

Intracellular Parasitism: It has been demonstrated that coagulase-positive staphylococci may survive for long periods within the cytoplasm of human and rabbit leukocytes and monocytes following phagocytosis.[71, 91] Such intracellular survival may play an important rôle in the clinical phenomenon of drug resistance,[53, 75] or may block host mechanisms responsible for the destruction of staphylococci.

Recent studies on staphylococcal bacteremia in rabbits suggest that viable staphylococci residing within circulating leukocytes may be responsible for the persistence of bacteremia following a large intravenous inoculum.[70]

Staphylococci are swiftly incorporated within leukocytes following intravenous injection, and remain viable within circulating cells. Such intracellular staphylococci appear to be selectively protected from removal mechanisms residing in the reticuloendothelial system which promptly remove extracellular staphylococci from the blood stream.

Thus staphylococci may have an intracellular phase of residence paralleling that of the tubercle bacillus, or other microörganisms known to survive within host cells.

The Nature of the Staphylococcal Lesion: One of the notable characteristics of staphylococcal infection is localized abscess formation. With the possible exception of infections in the very young, staphylococcal invasion results in rapid necrosis and destruction of tissue. Local host mechanisms tend to limit and contain staphylococcal infections by early thrombosis of capillaries in the area. Fibrin is deposited about the area of staphylococcal multiplication. It has been suggested that the coagulase production of staphylococci may promote early capillary thrombosis and fibrin barrier formation,[81] but the production of fibrin by coagulase has not been demonstrated in vivo.[30]

Local staphylococcal lesions are swiftly invaded by polymorphonuclear leukocytes, and rapid and striking phagocytosis of staphylococci ensues. The fully developed local lesion consists of a necrotic central area filled with dead and dying leukocytes and bacteria, surrounded and sharply demarcated by a fibroblastic wall. Viable leukocytes and bacteria lie within the abscess wall surrounding the central, nonviable core.

This characteristic localization of staphylococci in avascular, walled-off foci has been advanced as an explanation for the absence of demonstrable antibody response to staphylococcal disease, the chronicity of infection, and the failure of antimicrobials of high in vitro activity to eradicate staphylococcal infections. These concepts bear some examination.

It has been noted that serum antibody production is lacking in certain localized infections.[44] Hughes has demonstrated that fibrin membranes may act as a selective filter which will allow the passage of certain protein molecules but the retention of others.[45] It thus appears possible that local conditions at the site of infection may be such that tissue fluid nutrients may diffuse into local lesions, allowing the survival or multiplication of staphylococci, but antigenic components of the parasite may fail to reach the circulation. Such a phenomenon might explain the lack of demonstrable humoral immunity following staphylococcal infections, and their notorious tendency to relapse.

It seems reasonable to believe that serious tissue necrosis and walled local lesions make eradication of infection more difficult despite the administration of antimicrobials of high in vitro activity. Nevertheless, as indicated by McDermott,[58] it seems probable that this is a complex situation, rarely explained on the basis of simple failure of the antimicrobial drug to

reach the site of infection. Staphylococci, to survive in local lesions, require nutrients derived from the blood stream and extracellular fluids. It thus seems probable that antimicrobials present in such fluids must also arrive at the site of staphylococcal multiplication. Simple delivery of antimicrobial at the area of local infection does not, however, presume effective antimicrobial action at this site. Serum proteins and other tissue constituents may have a profound effect on the antimicrobial itself, the metabolic activities of the staphylococci, or both antimicrobial and parasite.

Dubos has stressed the fact that the local biochemistry of the lesion may differ profoundly from the over-all internal milieu of the animal host.[20] It has been demonstrated that there is intense glycolytic activity with the accumulations of large amounts of lactic acid at local areas of inflammation.[6] Glucose levels decline precipitously, oxygen is consumed, carbon dioxide levels rise, and local pH falls.[60] Such profound alterations in physiology occurring at the site of a staphylococcal lesion make it probable that drug-parasite relationships differ markedly from those observed in in vitro situations. Antimicrobial drugs may thus be inactivated, or staphylococci may exist in metabolic states in which they are relatively insusceptible to drug action at such local sites of infection.

Alterations in Host Susceptibility to Staphylococcal Infections: That a high degree of native resistance to staphylococcal infections exists is apparent from the relative infrequency of infection, despite the common presence of potentially pathogenic staphylococci within the anterior nares, or upon the skin surface. It has long been known, however, that certain alterations in the human host lead to a significant increase in the incidence of staphylococcal infections. Diabetics are notoriously susceptible to infections due to staphylococci. Situations of inadequate nutritional intake and filth have been thought to predispose to staphylococcal invasion, and staphylococcal infections were a troublesome problem in concentration camp victims suffering from severe dietary deficiencies and conditions of inadequate hygiene.[40] Certain local tissue alterations appear to predispose to staphylococcal infection. Furuncles and pyoderma are more common in individuals exposed to oil, grease, turpentine or other skin irritants. Pustular acne vulgaris appears to be related to excessive sebaceous gland activity, and staphylococcal pneumonia in the healthy adult is almost invariably preceded by true influenza.[13, 27, 61]

Recent studies suggest that this problem of altered host susceptibility can be approached experimentally. Dubos has shown that lactic acid has a marked antibacterial effect on staphylococci which is significantly decreased in the presence of ketone bodies.[19] Metabolic studies by Martin and his associates have shown that diabetic leukocytes produce less lactic acid from glucose than normal leukocytes.[56] Such observations suggest that diabetic ketosis may interfere with host mechanisms which operate to control staphylococcal multiplication in vivo.

Recent observations substantiate the clinical belief that the presence of a foreign body may profoundly alter local tissue resistance to staphylococcal multiplication. In quantitative studies, Elek [25] has demonstrated that the presence of a silk suture in the skin of human volunteers reduces the number of staphylococci required to produce local abscess formation ten thousand fold.

Smith and Dubos have studied the susceptibility of mice to systemic staphylococcal infection under varying conditions. These experiments show that host resistance can be swiftly and abruptly depressed by stress situations as varied as transient starvation, or the administration of thyroid or dinitrophenol.[77, 78, 79] Observations by Dubos and Schaedler further indicate that such heightened susceptibility may be transient, and readily reversible.[21] Such studies may lead to the identification of specific biochemical alterations reducing host resistance which are subject to manipulation.

Immunity to Staphylococcal Infections

Does the human host develop antistaphylococcal immunity? The striking differences in the type of disease produced by staphylococcal infection in the young and in adults would suggest that immunity does arise. Staphylococci are a common causative agent of primary bacterial pneumonia and tracheobronchitis in childhood, and the most frequent cause of empyema in infants.[32] In contrast, staphylococcal pneumonia is a rarity in the adult population. Infants do not develop local abscesses with the same predictability as adults, but invasion of the blood stream is more common than in older age groups.[66] Acute osteomyelitis is almost exclusively a disease of youth.

Despite this pattern, suggesting the development of progressive immunity, certain individuals have repeated attacks of boils due to a single strain of staphylococcus, unmodified in severity over the course of months or even years. Experimentally, it has been shown that no change in skin response results from the repeated, spaced intracutaneous injection of a single strain of staphylococci.[25]

Staphylococcal infections are not, in general, followed by a demonstrable antibody response. As previously noted, immunization of experimental animals with staphylococcal exotoxin or coagulase leads to the development of humoral antibody titers, but both fail to protect animals against progressive staphylococcal disease following challenge.[10, 48]

Thus, to date, satisfying and clear evidence of immune mechanisms operative in staphylococcal infections has not been demonstrated by classic immunologic methods, although there is excellent clinical evidence to support the belief that a degree of immunity is acquired during life.

The Epidemiology of Staphylococcal Infections

Coagulase-positive staphylococci are carried within the anterior nares or upon the skin of the majority of healthy adults. It has been amply demonstrated that staphylococci discharged into the air remain viable in bed-clothing and blankets, and are disseminated in dust particles. Colonies of potentially virulent staphylococci can be obtained from the air on wards or within well run operating rooms when personnel are present.[5, 14, 22] New born infants in hospital nurseries become nasal carriers within a few days, and frequently harbor the same phage types present in the nares of nurses and other personnel working around them.[73] Do such strains carried asymptomatically represent a serious threat when transmitted? There is considerable evidence to suggest that they do when transmitted to patients with open wounds or other situations of altered host resistance.[3, 5, 7, 9, 42, 83, 84]

However, there are some observations which suggest that the patient with an active staphylococcal infection is a more dangerous source of disease than the healthy nasal carrier. A recent report by Barber and Burston [4] indicates that, despite a high carrier state of a single phage strain of *Staphylococcus aureus* among nurses in a maternity unit, few infections were noted. When a nurse working in the unit developed a facial boil, two severe infections promptly occurred in infants within the nursery. Both the facial lesion and the infant infections were due to the same strain, which had been carried by the majority of nurses and infants for many months.

As phage typing has allowed better definition of the spread of staphylococcal infections, there are some indications to suggest that certain strains may be particularly prone to produce epidemic disease or to lead to certain types of staphylococcal infections.[59, 86] It would seem likely that the comparative virulence of various strains will now receive more meticulous study utilizing phage typing technics.

Antimicrobial Resistance: Penicillin-resistant strains of staphylococci were isolated from zero to 12% of patients harboring staphylococci in the period 1942 to 1944. Since this period, studies from widely scattered geographic areas indicate that the incidence of penicillin-resistant strains has steadily risen to 50 to 80% of the strains currently carried by selected groups of individuals within hospitals, and to a lesser extent in the population at large. This trend has been graphed in figure 2.

This epidemiologic pattern, and extensive studies on bacterial resistance, have indicated that staphylococci have a remarkable capacity for adapting to new environmental pressures produced by antimicrobial.[12] Clinically important penicillin resistance appears to develop principally through the selection of naturally occurring resistant mutants in response to penicillin in the environment.[17] The vast majority of these strains produce penicillinase.[47]

The selective emergence of antimicrobial-resistant strains has predictably followed the increasing use of each new antimicrobial with antistaphylococcal activity.[18, 53] On rare occasions, wide administration of an antimicrobial has not been followed by the recovery of strains insusceptible to the drug in use,[1] but, in general, there is little evidence to suggest that any new antimicrobial will overcome this problem.

Data reported by Knight and Holzer indicate clearly that the administration of antimicrobials assists in the colonization of the anterior nares and throat with phage group III "hospital" staphylococci which are resistant to

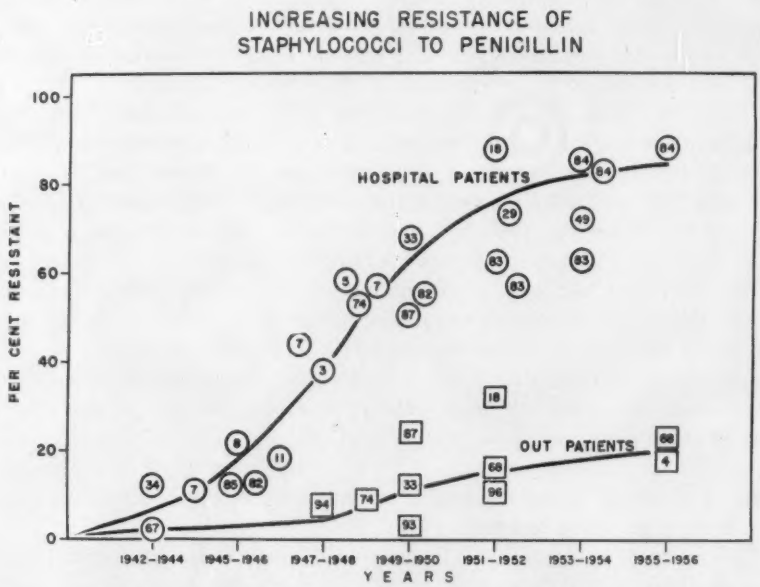


FIG. 2. The increasing penicillin resistance of staphylococci isolated from hospitalized patients and out-patients, 1942–1956. Note the continuing low incidence of penicillin-resistant strains obtained from nonhospitalized individuals. (The numerals within the circles and squares refer to bibliography number.)

the antimicrobials in use.[50] When tetracycline or penicillin was administered to groups of hospitalized patients for nonstaphylococcal disease, replacement of sensitive strains or the creation of the staphylococcal carrier state occurred in a high percentage of patients. In contrast, individuals on the same ward who received no antimicrobials did not show a consistent change in the carrier state and did not acquire resistant strains during the period of observation. Data adapted from this study are pictured in figure 3.

Of considerable interest in this study was the additional finding that carriers of more than a single phage type are rare. When resistant "hos-

pital" staphylococci appeared in the anterior nares, sensitive strains disappeared. This observation has been independently made by Gould and McKillop, who noted that it was rare to isolate more than a single phage type from one individual.[37] This phenomenon deserves further study. It is conceivable that the residence of one strain in the anterior nares may prevent the introduction of other, more virulent strains, and that such a phenomenon might be used practically in the management of the carrier state.

The Incidence of Staphylococcal Infections: Are serious staphylococcal infections actually more frequent than in the past? It is the impression of

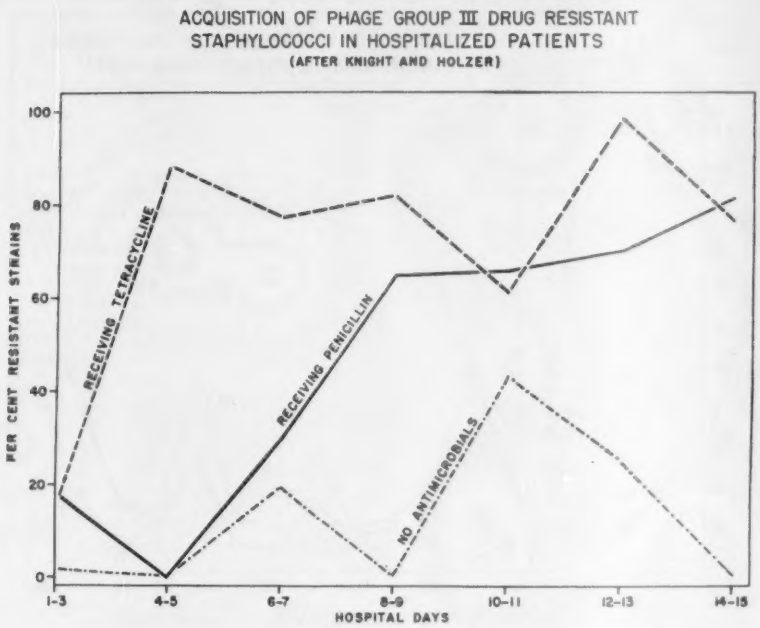


FIG. 3. The acquisition of phage group III antimicrobial-resistant staphylococci in hospitalized patients (after Knight and Holzer [50]).

many investigators within large hospital centers that an increasing number of patients die each year with staphylococcal infections.[64, 83, 84] In the absence of a central system of reporting staphylococcal disease, the actual incidence of staphylococcal infection is difficult to determine, and no statistical analysis of changes in the frequency of staphylococcal infections has appeared in the literature.

In an attempt to gain some information on this problem, the frequency of staphylococcal bacteremia in patients admitted to The New York Hospital over the past 16 years was investigated. During the years 1940 through

1955, 170 patients were admitted with or subsequently developed a staphylococcal bacteremia in the hospital. One hundred of these patients were children below the age of 16, and 70 cases of staphylococcal bacteremia were observed in adults. The yearly incidence of staphylococcal bacteremia in these two groups, with minor corrections for the number of admissions per year, is plotted in figure 4.

As indicated in figure 4, a significant difference is apparent in the incidence of staphylococcal bacteremia in these two groups of patients. Bacteremic disease was more frequent in children than in adults in the pre-

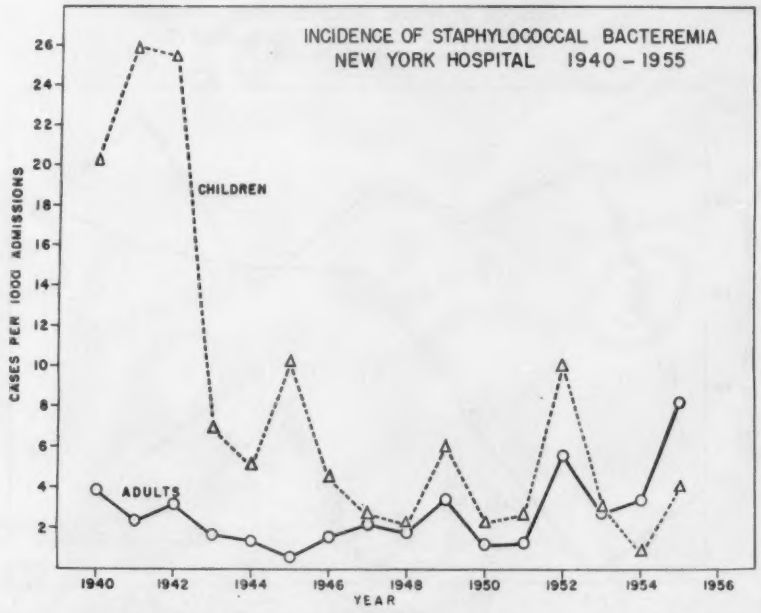


FIG. 4. The incidence of staphylococcal bacteremia in children under 16 years and adults admitted to The New York Hospital, 1940-1955.

antimicrobial era. However, the number of children with staphylococcal bacteremia definitely declined from 20 to 25 per 1,000 admissions (14 to 17 cases per year) in 1940–1942, to two to four per 1,000 admissions (one to three cases per year) in 1954 and 1955.

In contrast, the incidence of staphylococcal bacteremia in adults has remained relatively stable throughout this 16 year period, with a slight rise in 1955. In 1940–1942, three to five patients (2.4 to 3.9 per 1,000 admissions) were admitted with or subsequently developed staphylococcal bacteremia. Four, five and 13 patients with bacteremia (2.8 to 8.2 per 1,000) were seen in 1953, 1954 and 1955. Thus, definite differences in the relative

incidence of this disease in children and adults were noted, but little evidence of increasing frequency of staphylococcal bacteremia was obtained.

Study of disease associated with staphylococcal bacteremia has yielded further information which aids in understanding the differences in staphylococcal bacteremia in these two age groups. These data appear in table 1. Fifty-nine of the 100 children were admitted because of acute infections due to staphylococci developing outside the hospital. Of these, 25 had acute staphylococcal pneumonia with bacteremia, 23 had acute osteomyelitis, and 11 developed bacteremia from an infected skin focus. Only 25 children had other illness occurring in association with the staphylococcal infection.

TABLE 1

Clinical Differences in Staphylococcal Bacteremias in Children and Adults

	Children (100 cases)		Adults (70 cases)	
	Number	Per Cent	Number	Per Cent
1. Occurred during course of acute staphylococcal disease	59	59	10	14.3
A. Staphylococcal pneumonia	25	25	3	4.3
B. Acute osteomyelitis	23	23	3	4.3
C. From primary skin focus	11	11	4	5.7
2. Associated with serious underlying disease	25	25	60	85.7
	Serious congenital defect 11		Exfoliative dermatitis 13	
	Exfoliative skin disease 5		Diabetes 10	
	Erythroblastosis 4		Leukemia, Lymphoma, Metastatic carcinoma 9	
	Leukemia 2			
	Rickets 1		Valvular heart disease 8	
	Ulcerative colitis 1		Pyelonephritis 8	
	Congenital hemolytic icterus 1		Postoperative complication 5	
			Lupus erythematosus 2	
			Severe trauma 2	
			GI hemorrhage 2	
			Transverse myelitis 1	
3. Mortality	36	36	47	67.1

In contrast, 60 (or 85.7%) of the 70 adults had serious associated disease, which frequently had direct bearing on the subsequent staphylococcal bacteremia. Ten patients had long-standing diabetes associated with serious peripheral vascular disease. Exfoliative dermatitis, malignancies, serious valvular disease, pyelonephritis and complicated operative problems commonly caused the admission of adults, and preceded the onset of staphylococcal bacteremia which generally occurred within the hospital. Indeed, many of the patients developing staphylococcal bacteremia in the last five years were patients who would not formerly have survived from their primary disease.

The mortality of staphylococcal bacteremia occurring in adults has remained disturbingly unaltered by antimicrobials in this series. As noted in table 2, nine of 13 patients seen prior to the use of penicillin died, a mortality of 69%. This compares reasonably with the mortality of 82% reported by Skinner and Keefer during the period preceding antimicrobial therapy.[76]

TABLE 2

Mortality with Staphylococcal Bacteremia
1940–1955

Period	Adults			Children		
	Number of Patients	Number of Deaths	Mortality	Number of Patients	Number of Deaths	Mortality
1940–1942	13	9	69%	49	18	37%
1943–1948	17	10	59%	26	13	50%
1949–1955	40	28	70%	25	5	20%
Totals	70	47	67.1%	100	36	36%

In contrast to the observations of Hall and Spink,[39] there was little change in the over-all mortality during the early years of penicillin treatment, despite the high incidence of penicillin-susceptible strains. During the last seven years, 70% of patients with persistent staphylococcal bacteremia have died.

Mortality statistics alone are nevertheless misleading, and do not indicate the change in the type of patient now succumbing with staphylococcal bacteremia. The majority of patients studied by Skinner and Keefer were under 30 years of age, and acute staphylococcal illness caused their admission to the hospital. Since 1943, patients acquiring staphylococcal bacteremia in this hospital have characteristically been over 50, and serious nonstaphylococcal disease has required their hospitalization. Staphylococcal bacteremia has occurred within the hospital as a terminal event in such illness.

As the incidence of bacteremia in children has declined, mortality has also fallen in this series. Only five of 25 children with staphylococcal bacteremia admitted during the years 1949 to 1955 have succumbed with their disease. Serious associated disease was present in four of these patients.

Does an analysis of bacteremic staphylococcal infections give a true index

of the problem? As previously indicated, adults characteristically focalize staphylococcal infections, and the majority of staphylococcal infections are not commonly associated with invasion of the blood stream. In pre-antimicrobial days, staphylococcal pneumonia was unusual in adults except during influenza epidemics. It has been our impression that staphylococcal pneumonia has been seen in greater incidence in recent years. An analysis

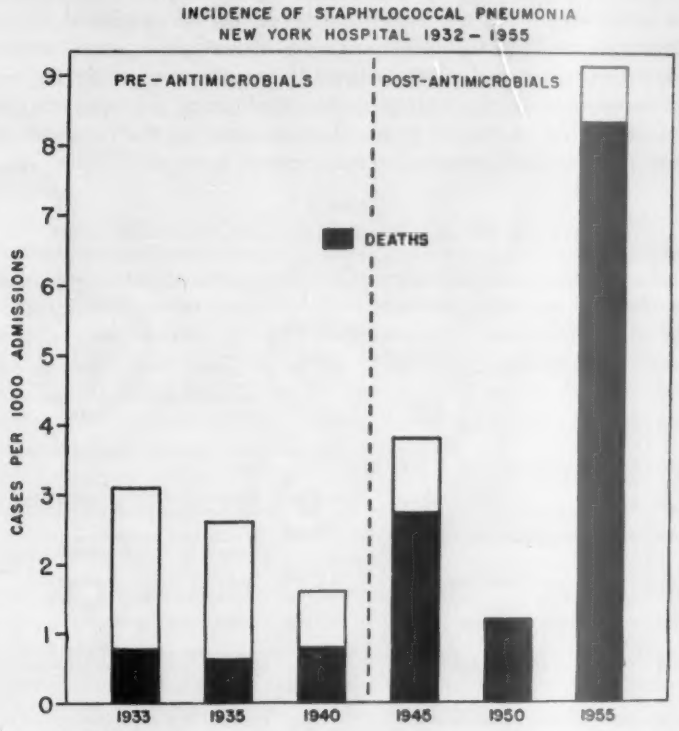


FIG. 5. The incidence of staphylococcal pneumonia in adults admitted to The New York Hospital, 1933–1955. There is a suggestive increase in staphylococcal pneumonia occurring during the antimicrobial era. Staphylococcal pneumonia has been a common terminal event in other serious illness in recent years. Mortality has been high in this group.

was thus made of all adults with staphylococcal pneumonia seen in The New York Hospital in six different years from 1933 to 1955. The records of patients with staphylococcal pneumonia admitted during the years 1933, 1935 and 1940 (antimicrobials unavailable) were compared with those admitted during 1945, 1950 and 1955.

As noted in figure 5, the number of patients with staphylococcal pneumonia per 1,000 admissions appears to have increased since the availability

of effective antimicrobial drugs. Ten patients with staphylococcal pneumonia were seen during the years 1933, 1935 and 1940, in contrast to 21 patients with this disease hospitalized during 1945, 1950 and 1955.

Review of these records reveals a striking difference in the type of disease pattern observed in these two groups. Six (or 60%) of the pre-antimicrobial admissions were occasioned by acute staphylococcal pneumonia occurring clinically as primary disease, principally in young adults. Three patients admitted during the pre-antimicrobial period developed metastatic staphylococcal pneumonia during the course of a staphylococcal bacteremia, and one patient developed staphylococcal bronchopneumonia during an episode of congestive failure. Despite the development of empyema in five patients, only three of the 10 died. Two of these deaths occurred among the three patients with primary staphylococcal bacteremia.

TABLE 3

Changing Host Setting in Which Staphylococcal Pneumonia Occurs

Pre-Antimicrobial Period (1933, 1935, 1940)				Antimicrobial Period (1955)			
Case	Age Sex	Clinical Setting	Outcome	Case	Age Sex	Clinical Setting	Outcome
1	33F	Septic abortion, bacteremia, pneumonia	D	1	51F	Carcinoma kidney, metastatic, liver, lungs, lymph nodes. Intestinal obstruction, terminal pneumonia	D
2	26M	Primary pneumonia—empyema	L	2	55F	Acute leukemia, terminal pneumonia	D
3	47M	Primary pneumonia—empyema	L	3	58F	Nephrolithiasis, uremia operation, terminal pneumonia	D
4	39F	Primary pneumonia	L	4	38F	Myelogenous leukemia—splenectomized, terminal pneumonia	D
5	21F	Primary pneumonia—empyema	L	5	36F	Diabetes, nephropathy, uremia, terminal pneumonia	D
6	33F	Skin abscess, bacteremia, pneumonia	D	6	32F	Primary staph. pneumonia	L
7	28M	Primary pneumonia—empyema	L	7	60M	Carcinoma, lung, metastatic to liver, kidney, pancreas, terminal pneumonia	D
8	45M	Rheumatic heart disease, congestive failure, bronchopneumonia and empyema	L	8	79F	Gastric ulcer, pyelonephritis, uremia, ASCVD, bronchopneumonia	D
9	52M	Hand infection, bacteremia, pneumonia	L	9	64F	Diabetes, acidosis, pyelonephritis, uremia, chronic bronchitis, bronchopneumonia	D
10	38F	Primary pneumonia, rheumatic heart disease	D	10	42M	Advanced pulmonary emphysema, respiratory acidosis. O_2 for 2 years, lobectomy, terminal pneumonia	D
				11	72M	Paralysis agitans, bedridden 6 years, admitted with pneumonia	D
				12	34M	RHD, MS, MI, AS, AI. Hufnagel valve, postoperative mediastinitis, pneumonia	D
				13	72M	Erythema multiforme bullosum pyelonephritis, uremia, ACTH, undiagnosed pneumonia	D
Average age = 36.2			Mortality = 30%	Average age = 53.4			Mortality = 92.3%

In striking contrast are the 21 patients with staphylococcal pneumonia seen in 1940, 1945 and 1955. Only four of these patients were admitted with clinically primary pneumonia. The remaining 17 patients had, without exception, serious, advanced debilitating disease. The average age of these patients was considerably older (56.3 years in contrast to 36.2 years), and staphylococcal pneumonia occurred as a terminal event. Only six patients with staphylococcal pneumonia seen in the years 1945, 1950, and 1955 survived, representing a mortality of over 70%.

Nevertheless, review of these cases makes it difficult to assign the staphylococcus a primary rôle in their deaths. It has seemed progressively apparent, upon review of our cases, that the staphylococcus now occupies the place formerly held by the pneumococcus in producing terminal infection in patients protected against sensitive strains of microörganisms by antimicrobial therapy.

Table 3 compares the histories and outcome of the 10 patients with staphylococcal pneumonia seen in 1933, 1935 and 1940 with the 13 patients with staphylococcal pneumonia seen during 1955.

Other investigators have indicated that postoperative staphylococcal infections are an increasing problem in surgical units. Howe has made a careful retrospective analysis of the incidence of wound infections in the Massachusetts Memorial Hospitals during the years 1949 to 1953 [42] and, more recently, has extended this survey through 1955.[43] Figure 6 has been constructed from his reported data.

As illustrated in figure 6, the incidence of postoperative wound infections steadily increased, from approximately 1% in 1949 to a high of 10% early in 1954. Analysis of the predominant microörganisms isolated on culture from such wounds revealed an increase in the frequency of hemolytic *Staphylococcus aureus* as the predominating infecting microörganism from 57.1% in 1949 to 80.6% in 1953. A survey of the staphylococcal carrier rate in over 100 personnel and patients in this study revealed that 99.2% of these individuals yielded *Staphylococcus aureus* from the anterior nares or skin. Almost 80% of these strains were penicillin-resistant.

Late in 1954, vigorous measures were instituted to prevent cross infections due to staphylococci. These included the more sparing use of antimicrobial prophylaxis in clean operative cases, double masking during long operations, masks and gloves for the changing of operative dressings, special "septic" sets and occlusive dressings for the treatment of infected wounds, and other procedures designed to prevent cross inoculation of staphylococci from staff to patients.

Following the institution of such procedures, postoperative infection rates fell to 2% in 1955. Cultures obtained from personnel indicated reduction in the staphylococcal carrier state from over 99% to 75%, and only 62% of the staphylococcus strains isolated were found to be penicillin-

resistant. Staphylococci declined as the predominating microörganisms in wound infections during this period.

Similar studies have been reported by Blowers in a chest surgery unit in England.[9] Postoperative wound and intrathoracic infections due to penicillin-resistant staphylococci reached an incidence of 10.9%, forcing the temporary closure of the unit. With the establishment of precautions designed to reduce airborne spread of staphylococci, there was a concomitant decline in the incidence of infection to 3.9% and a sharp reduction in staphylococcal carrier rates among personnel.

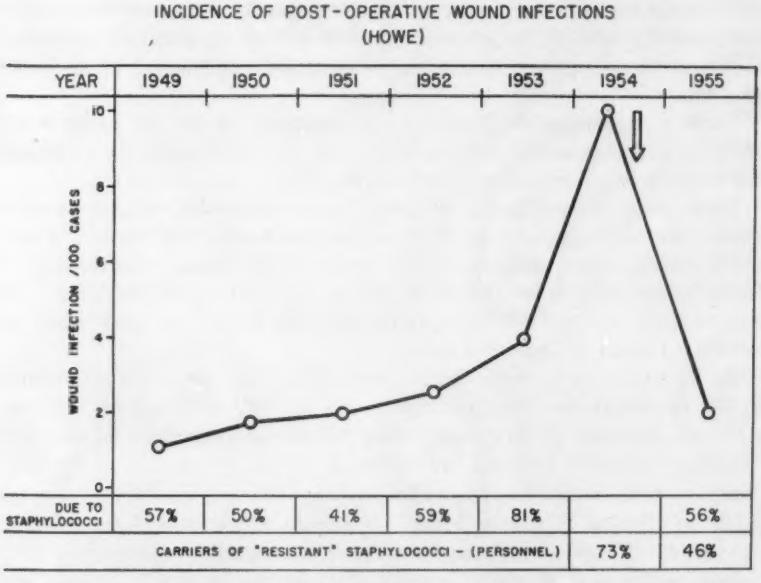


FIG. 6. The incidence of postoperative wound infections on a surgical unit, 1949–1955. With the institution of measures designed to limit cross infection in 1954, wound infections declined in frequency (after Howe [42, 43]).

CLINICAL PROBLEMS IN STAPHYLOCOCCAL INFECTION, 1956

It has been our experience that the clinical problems in staphylococcal infection now fall into two rather distinct groups. Patients admitted from the community with acute, deep-seated staphylococcal infections constitute the first and lesser group. It has been our impression that such acute staphylococcal infections are less frequent than in the days before antimicrobials were available, and the summary of our experience presented in figures 4 and 5 supports this view. As might be expected from the significantly lower incidence of resistant strains of staphylococci in nonhos-

pitalized populations, the majority of these infections occurring in the community have been due to antimicrobial-sensitive strains of staphylococci.

Figure 7 summarizes the clinical course of a 22 year old woman with known rheumatic heart disease admitted with an acute illness characterized by 48 hours of headache, fever and profound malaise, initially diagnosed as influenza. Five blood cultures taken during the initial 36 hours revealed the growth of a coagulase-positive staphylococcus which was sensitive to 0.1 unit of penicillin and 0.4 μg. of streptomycin per milliliter. This patient made a prompt and complete recovery on six weeks of combined penicillin-dihydrostreptomycin therapy and has remained well over a three year period

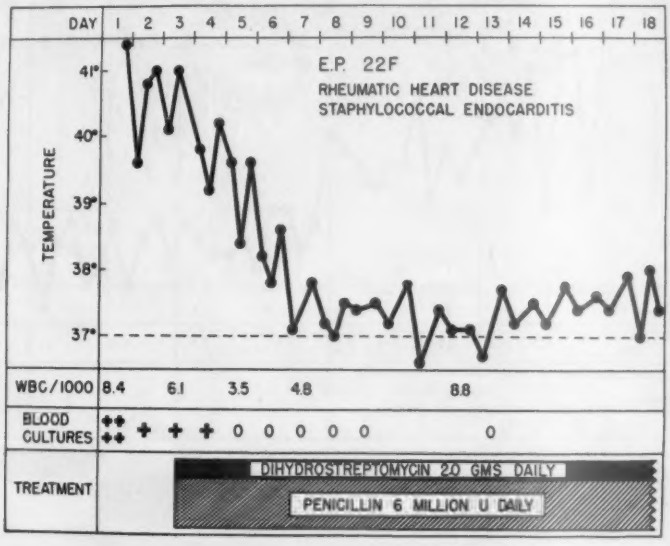


FIG. 7. Acute staphylococcal endocarditis in a 22 year old woman with rheumatic heart disease. The staphylococcus recovered was sensitive to all antimicrobials in vitro. Complete recovery followed six weeks of combined penicillin-dihydrostreptomycin therapy.

of observation. A striking change in the character of her systolic apical murmur to a high-pitched, cooing murmur made the diagnosis of endocarditis quite certain.

Figure 8 represents the clinical response of a 23 year old medical student admitted with an acute staphylococcal pneumonia following type B influenza. The staphylococcus isolated from the sputum and empyema fluid proved to be extremely sensitive to penicillin, streptomycin and chlortetracycline. Despite a stormy course, with the rapid development of empyema, this young man made a complete recovery.

Acute osteomyelitis is now a rarity on our medical wards. Our single

case this year, a 16 year old boy, had a bacteremia due to a strain of *Staphylococcus aureus* highly sensitive to all commonly used antimicrobial agents.

The second group of patients with serious staphylococcal infections represents an increasing therapeutic problem. These are individuals with serious illness requiring hospital admission who receive numerous medical and surgical diagnostic and therapeutic procedures.

Such individuals are generally in the older age group. As indicated in tables 1 and 3, these patients are frequently altered, abnormal and seriously

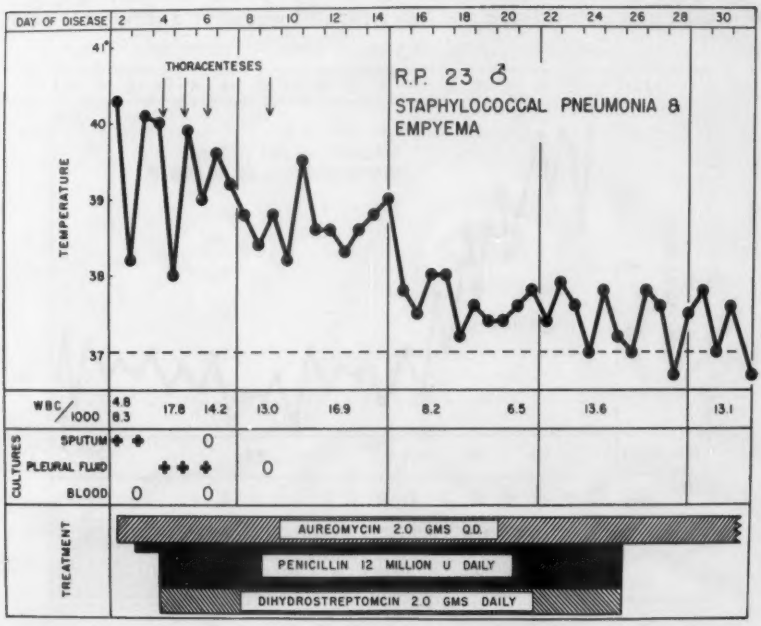


FIG. 8. Acute staphylococcal pneumonia and empyema in a 23 year old male. Staphylococci isolated from sputum and pleural fluid were sensitive to all antimicrobials in vitro. Treatment with penicillin, dihydrostreptomycin and Aureomycin resulted in complete recovery.

ill hosts. In the majority of cases, serious staphylococcal infections arise in the hospital from obvious skin foci, open wounds, or instrumentation of the genitourinary tract under the umbrella of prophylactic antimicrobial therapy.

In certain measure, the incidence of serious staphylococcal infection appears to parallel the seriousness of the underlying illness. At Memorial Hospital, where in-patients are almost exclusively individuals with malignancy receiving extensive medical or surgical therapy, the incidence of staphylococcal bacteremias has been over five times that observed in our own

hospital, despite a similar orientation toward problems of infection.[15] Four patients, admitted during the last year, serve to illustrate the problems in management of staphylococcal infections in this group of patients.

Figure 9 illustrates the course of an antimicrobial-resistant staphylococcal bacteremia occurring in a 43 year old woman with severe exfoliative dermatitis. Bacteremia appeared during treatment with ACTH and tetracycline. Despite the administration of all antimicrobials then available, death occurred on the twenty-sixth hospital day.

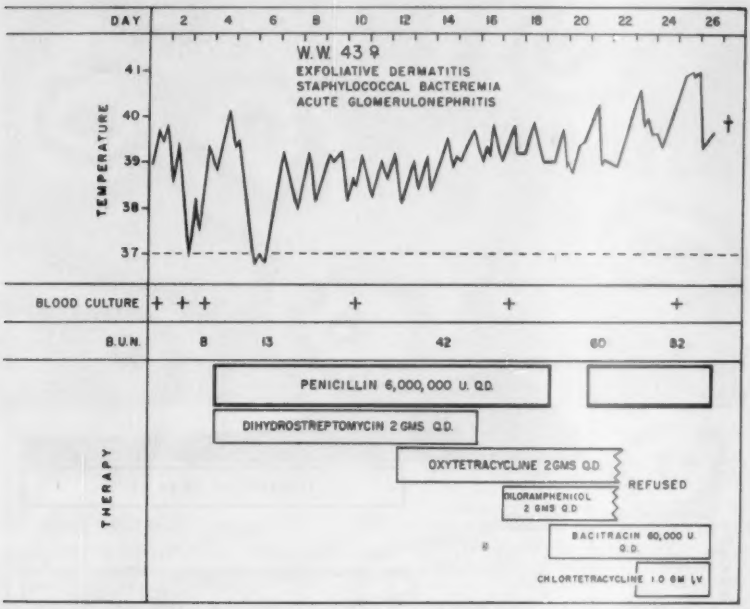


FIG. 9. Antimicrobial-resistant staphylococcal bacteremia occurring in a hospitalized woman receiving ACTH for severe exfoliative dermatitis. Death ensued despite the administration of penicillin, dihydrostreptomycin, oxytetracycline, chloramphenicol, bacitracin and chlortetracycline.

In the last four years six cases of staphylococcal bacteremia arising in patients with exfoliative dermatitis have been admitted to this hospital. Two of these individuals have had three and four separate episodes of staphylococcal bacteremia, respectively. It has been our impression that the use of ACTH and cortisone has contributed to this problem, and this has been recently reported in the literature.[63] Nevertheless, review of all of the patients admitted to The New York Hospital with exfoliative dermatitis during the last 16 years has revealed that 13 of 51 patients, or approximately 25%, have developed staphylococcal bacteremias. Only four of these patients were receiving hormonal therapy.

In a number of patients with dermatitis, staphylococcal bacteremia has run an atypical chronic course, with low grade fever and few signs of toxicity. In each of these cases there has been considerable argument regarding the significance of the positive blood cultures taken through exfoliating, obviously infected skin. Nevertheless, nine of these 13 patients have died, with obvious staphylococcal infection evident at autopsy. This correlation between denuding skin disease and the development of staphylococcal bacteremia merits further study.

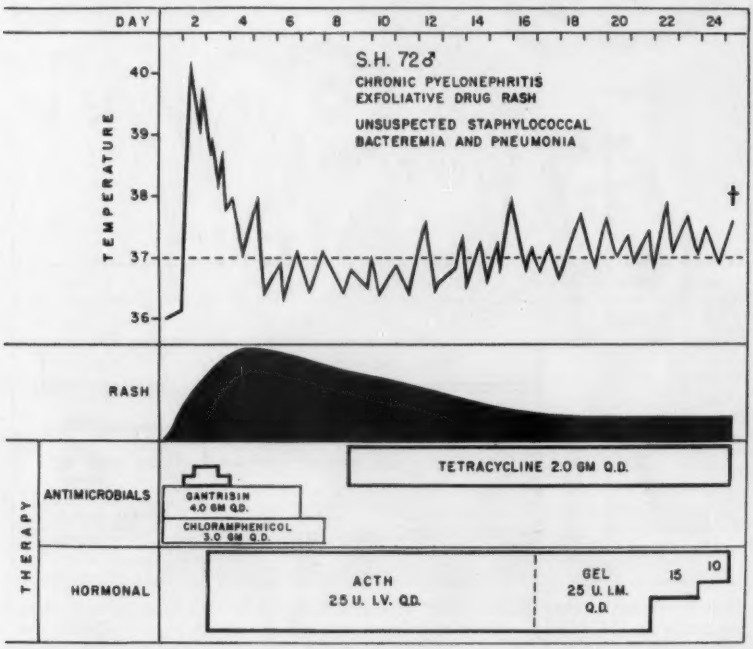


FIG. 10. Death due to unrecognized staphylococcal pneumonia and probable bacteremia in a 72 year old man receiving ACTH and tetracycline for an exfoliative skin rash. No clinical symptoms or signs of infection preceding death.

Figure 10 illustrates the masking of extensive staphylococcal pneumonia in a patient with pyelonephritis and erythema multiforme bullosum receiving ACTH and tetracycline. This patient, who was totally asymptomatic, without cough, elevation of his respiratory rate or leukocytosis, suddenly died while being turned in bed. Autopsy revealed the extensive bronchopneumonia with multiple abscess formation pictured in figure 11. Cultures obtained from the lungs grew a pure culture of hemolytic *Staphylococcus aureus* which was resistant to over 50 μg. of tetracycline.



FIG. 11. Cross-section of left lung of patient S. H. (figure 10), showing edema and prominent abscess formation. Coagulase-positive staphylococci, resistant to over 50 μg. of tetracycline, were cultured from the thick purulent material contained in the abscess cavities.

Serious infections secondary to operative procedures are frequently due to antimicrobial-resistant staphylococci. Figure 12 illustrates the course of a 37 year old woman who developed acute osteomyelitis and bacteremia following curettage of a benign bone cyst and the packing of the cavity with bone chips obtained from a bone bank. Despite the administration of erythromycin, to which the staphylococcus isolated was sensitive, she became progressively ill. Extensive drainage of the local focus resulted in prompt improvement and eventual recovery.

Enterocolitis, with marked fluid loss and the rapid development of shock, is now a well known clinical syndrome. Pure cultures of staphylococci are frequently obtained from the stools during the disease. Dearing and his associates have clearly indicated that this entity was well recognized prior to the advent of broad spectrum antimicrobials.[16] Nevertheless, recent outbreaks of staphylococcal enterocolitis and death in chinchillas receiving Aureomycin in foodstuffs, an entity not seen prior to the use of antimicrobials in these animals, suggest that antimicrobials may have some causal relationship.[97]

A recent fatal case of staphylococcal enterocolitis occurring in a 72 year old man receiving prophylactic penicillin and streptomycin for a tongue biopsy is illustrated in figure 13. During his final 12 hours of life, pure pus containing immense numbers of staphylococci was passed per rectum. The appearance of the terminal ileum and cecum at autopsy is illustrated in figure 14.

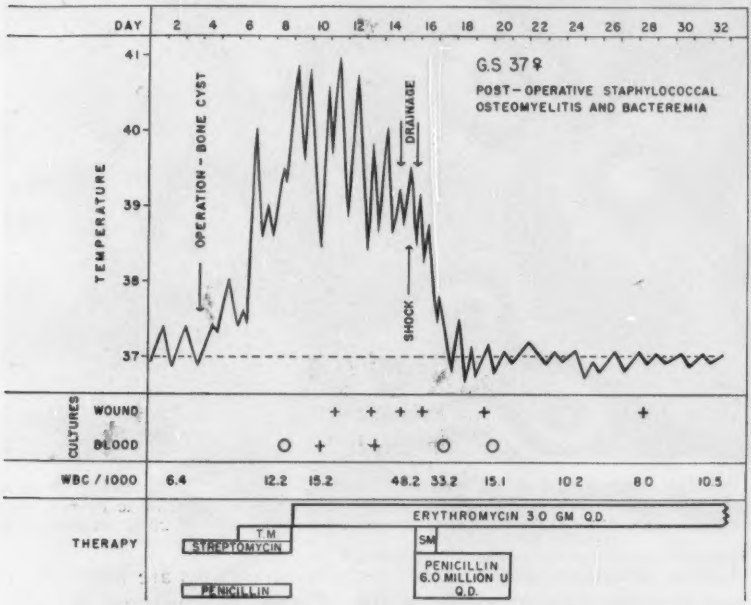


FIG. 12. Osteomyelitis and bacteremia following curettage and bone chip packing of a benign bone cyst. This infection appeared during prophylactic penicillin-streptomycin therapy. Staphylococci isolated from the blood and bone were resistant to penicillin and streptomycin but sensitive to erythromycin. Prompt recovery followed local drainage.

TREATMENT OF STAPHYLOCOCCAL INFECTIONS

In patients admitted with acute, deep-seated infections due to drug-susceptible staphylococci, aqueous penicillin has remained the drug of choice. Although increasing penicillin resistance of a single staphylococcal strain persistently isolated during therapy has been reported,[28, 41] we have never seen it occur in the management of closed staphylococcal infections. In vitro studies on enterococci have suggested that the combination of penicillin and streptomycin possesses greater bactericidal activity than either drug alone.[69] Consequently, these patients have generally received these two drugs in combination, using 6 to 12 million units of aqueous penicillin, and 1 to 2 gm. of streptomycin or dihydrostreptomycin daily. Such in-

fections generally respond well to antimicrobial therapy when other serious disease is not present. Nevertheless, occasional patients develop extensive necrotic local lesions in the lung or kidney, particularly if effective therapy is delayed, which leads to chronic disease or death.

We have occasionally encountered patients with highly susceptible staphylococcal infections who have nevertheless failed to respond to what was considered appropriate antimicrobial therapy on the basis of in vitro susceptibility studies. Figure 15 illustrates the course of a seven year old

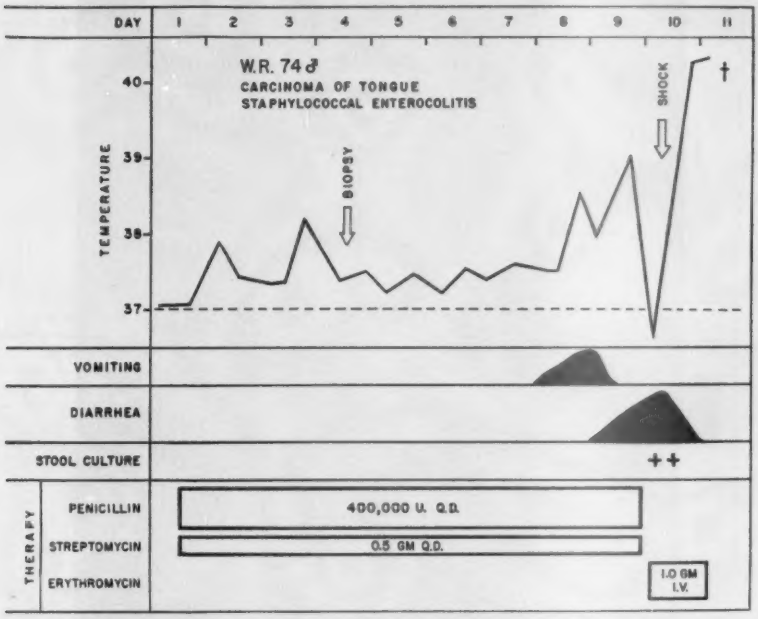


FIG. 13. Acute, fatal enterocolitis appearing during the prophylactic parenteral administration of penicillin and streptomycin. Gross pus containing immense numbers of staphylococci was passed per rectum during last 12 hours of life.

boy with endarteritis due to a coagulase-negative *Staphylococcus albus* which was exquisitely sensitive to penicillin, streptomycin and the tetracyclines. Despite five weeks of intensive therapy, blood cultures remained positive and he remained febrile. The administration of novobiocin,* in conjunction with streptomycin, resulted in prompt control of his infection, and allowed the successful ligation and resection of his persistent ductus arteriosus in his sixteenth hospital week.

In individuals with other serious disease states who acquire staphylo-

* Novobiocin was generously supplied by Dr. J. A. Dugger, The Upjohn Company, Kalamazoo, Michigan.

coccal infections within the hospital, antimicrobial therapy has been discouraging. The majority of these infections have been due to staphylococci manifesting high resistance to penicillin, streptomycin and the tetracycline drugs. Many of these patients have impaired renal function, as



FIG. 14. Terminal ileum and cecum of patient W. R. (figure 13), showing marked edema, lymphoid hyperplasia, and loss of epithelium. Microscopically, the submucosa was infiltrated with neutrophils, plasma cells and gram-positive cocci.

stressed by Spink,[88] which has narrowed the choice of possible antimicrobial agents. In this situation, therapy has become a complex problem, frequently unsolved by the use of antimicrobials alone.

Although antimicrobial-resistant strains constitute a serious problem,

we are in agreement with Knight and Collins [49] that drug resistance per se has rarely been the cause of our therapeutic failures in such patients. With very few exceptions, such antimicrobial-resistant staphylococci have been found susceptible in vitro to one of the newer antimicrobial agents with high antistaphylococcal activity. During the last two years, over 60% of strains isolated from infections have proved susceptible in vitro to erythromycin and chloramphenicol. These two agents have been less widely used in our hospital than other antimicrobial agents. In certain staphylococcal infec-

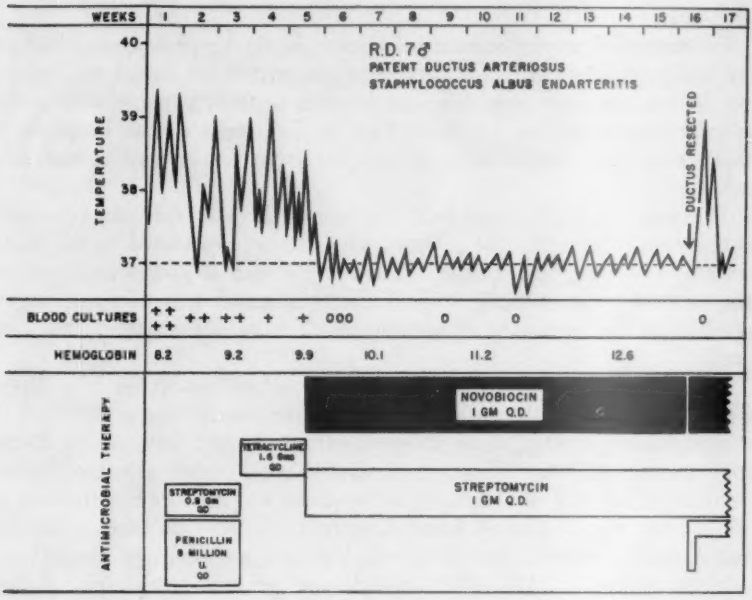


FIG. 15. *Staphylococcus albus* endarteritis occurring in a seven year old boy with a patent ductus arteriosus. Despite high in vitro sensitivity of the staphylococcus to all antimicrobials, positive blood cultures persisted for five weeks on treatment with penicillin, streptomycin and tetracycline. Administration of novobiocin resulted in clinical cure, and allowed ligation and resection of the ductus.

tions, uncomplicated by other serious disease, these antimicrobials have been successful in controlling progressive staphylococcal infection. Most of the staphylococci recently studied in our laboratory have been susceptible to bacitracin in vitro. However, the high incidence of renal impairment in the hospital group acquiring staphylococcal infections has limited our use of this agent.

It has been our impression, and that of Fisher and his associates,[31] that many patients with penicillin-resistant staphylococcal infections respond to penicillin therapy. Studies in the laboratory indicate that most staphylo-

coccal strains are not homogeneous in their antimicrobial susceptibility. In recent observations on a strain inhibited by 3.1 units of penicillin per milliliter in conventional serial dilution studies, over 90% of the microbial population was unable to grow in 0.1 unit per milliliter. Nevertheless, occasional clones from the same culture grew in 10,000 units per milliliter.[57] It thus seems probable that the majority of staphylococci in a microbial population may be affected by penicillin, despite the insusceptibility of some microorganisms. The suppression of most of the staphylococcal population may be sufficient to tip the balance for the host in the management of certain infections.

Treatment of staphylococcal infections should be prolonged. Relapses have occurred when effective antimicrobials have been halted in less than three to four weeks. It is now our practice to treat patients with serious staphylococcal infections for from four to six weeks in the hospital, frequently continuing suppressive therapy for from one to two months after discharge.

The surgical drainage of local staphylococcal abscesses has resulted in the recovery of a number of patients who had not responded to the administration of antimicrobials alone. The more favorable prognosis of patients with surgically approachable staphylococcal infection was noted during the pre-antimicrobial period, and antimicrobials have not changed this situation.[76, 83]

Recent experimental studies by McCune and his associates bear directly on this problem. In the treatment of an experimental mouse infection due to staphylococci susceptible to streptomycin, prolonged therapy for 30 days rarely resulted in the eradication of staphylococci residing in the kidney.[57] A striking difference in antimicrobial response was noted when therapy was withheld for a period of 54 hours (figure 16). At this time, when early renal abscess formation had occurred, kidney populations of staphylococci remained at levels of 1,000,000 staphylococci per milliliter despite the continuous administration of streptomycin for 30 days. Staphylococci isolated from mouse tissues at this time remained as sensitive to streptomycin as the initial inoculum.

These studies have important clinical implications. It seems probable that local abscess formation has ensued prior to the initiation of therapy in many human staphylococcal infections. The experimental demonstration that active antimicrobials are ineffective in the presence of abscess may have bearing on the refractory nature of many human infections and the high incidence of relapse following short-term antimicrobial therapy.

Staphylococcal infections acquired in the hospital have originated from an obvious skin focus or a recent surgical wound in over 60% of the cases in this series. Colonization of skin and wound areas by staphylococci appears to be aided by the prophylactic administration of antimicrobials. Vigorous attempts are thus being made to decrease the indiscriminate use

of antimicrobials in patients without infection, and to pay serious attention to all local foci from which staphylococcal infection may disseminate. The isolation of patients with exfoliative skin disease or other denuded surface sites which may be colonized with antimicrobial-resistant strains of staphylococci is now being seriously considered.

There are some indications that the incidence of hospital staphylococcal infections can be reduced by measures designed to prevent cross-inoculation

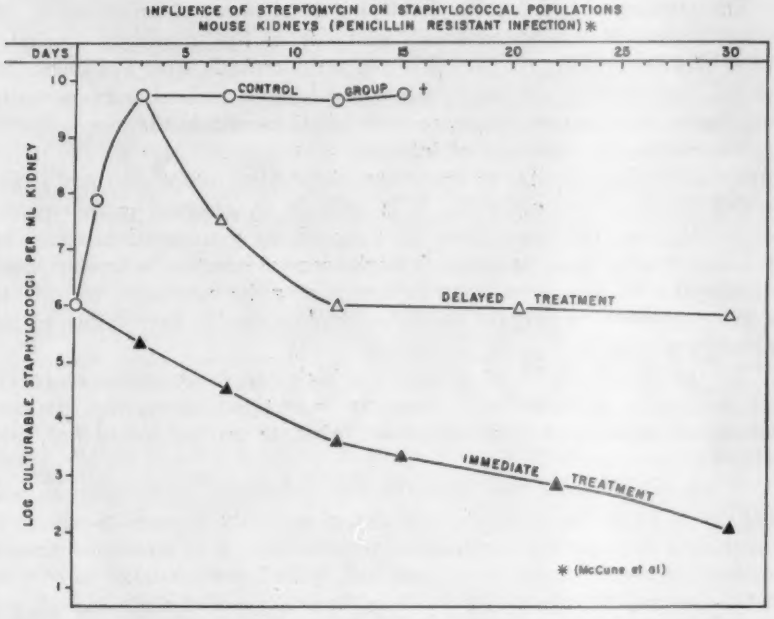


FIG. 16. The influence of streptomycin on staphylococcal populations of mouse kidneys (penicillin-resistant infection). Despite the administration of streptomycin for 30 days, culturable staphylococci of original streptomycin susceptibility persisted in the kidneys. When treatment was delayed for 54 hours, 30 day treatment failed to reduce kidney staphylococcal populations below 1,000,000 units per milliliter of kidney (adapted from McCune, Dineen and Batten [87]).

of microörganisms.[4, 9, 42] The more judicious use of potent antistaphylococcal drugs, particularly in prophylactic situations, may also reduce the problem of antimicrobial-resistant strains within hospital centers.

Our observations suggest that established staphylococcal infections will continue to cause death in a number of patients already suffering from other serious disease. New approaches to the problems of altered host resistance and the spread of staphylococci would appear to offer more promise than new antistaphylococcal agents for the treatment of established infection.

Concluding Remarks

Staphylococcal infections have assumed a position of great prominence during the past decade. Despite the inclusion of staphylococci with other microörganisms producing acute infections in man, it is clear that there are unique features in staphylococcus-host relationships which set this microorganism apart as a highly adaptable parasite capable of surviving within human serum and phagocytic cells, and adjusting to meet unfavorable new environments, including human tissues bathed in antimicrobials.

The population group now developing staphylococcal infections is, in certain important ways, a different group from that acquiring staphylococcal infections during the period before antimicrobials were available. In general, these patients are individuals with advanced, serious and potentially fatal disease who acquire staphylococcal infections within the hospital.

The increasing incidence of infection in this group due to strains of staphylococci unsusceptible to many antimicrobial agents constitutes a disturbing problem. Nevertheless, it is difficult to assign our therapeutic failures to drug resistance alone in a significant number of cases. The basic underlying disease upon which staphylococcal infection is superimposed is commonly the important factor in determining the outcome. In this era of antimicrobial coverage, the staphylococcus appears to have displaced the pneumococcus as the invader in terminal illness.

The healthy human host possesses a high degree of resistance to infections due to staphylococci. There are recent indications that the circumstances which lead to altered host resistance can be approached, and defined experimentally.

It appears probable that staphylococcal infections, once initiated, will continue to cause the death of a number of seriously ill patients who now constitute a large part of our hospital populations. It is doubtful that new antimicrobials will alter this situation, and, indeed, there is much to suggest that antimicrobials have played a rôle in the emergence of staphylococci as a troublesome hospital problem. More information is needed about the factors which increase host susceptibility to staphylococcal infection. Procedures which will effectively reduce staphylococcal carrier rates, and cross-inoculation of staphylococci within hospitals, also require better definition.

The therapy of established staphylococcal infections has received the major emphasis in recent years. Methods which may prevent staphylococcal infections in altered, abnormal hosts now merit equally serious investigation in the hope of reducing the hospital incidence of staphylococcal disease.

Summario in Interlingua

Infectiones staphylococcal occupa un position de crescente importantia in centros hospitalari in omne partes del mundo in consequentia de lor responsa pauco satisfactori a therapias antimicrobial.

Certe proprietates del relation inter le staphylococcos e lor hospite suggere que iste micro-organismos differe fundamentalmente ab altere coccos Gram-positive con que illos es generalmente classificate. Iste proprietates include le production del enzyma coagulase del parte del staphylococcos, lor capacitate de superviver in phagocytos del hospite, le natura chronic del infectiones staphylococcal, e le absentia de un demonstrabile immunitate anti-staphylococcal.

Un del plus frappante proprietates del staphylococcos es le emergentia de racias resistente a omne nove agente antimicrobial con activitate anti-staphylococcal. Studios in patientes hospitalisate indica que le uso de agentes antimicrobial es definitivemente implicate in le acquisition de tal staphylococcos a resistentia contra agentes antimicrobial.

Le revista del infectiones staphylococcal occurrente durante le passate 16 annos in un sol grande hospital revela que le numero del juveniles admittite con bacteremia staphylococcal ha decrescite progressivemente. Durante le mesme priodo le incidentia de bacteremia e pneumonia staphylococcal in adultos ha crescite levemente. Studios per altere autores indica que le incidentia de infectiones postoperatori de vulneres, causate per staphylococcos, ha definitemente crescite in le curso del passato recente.

Iste alterationes del incidentia pare esser debite a un alteration in le typo de patiente qui acquire infectiones staphylococcal depost que agentes antimicrobial ha devenite disponibile. Ante le advento del agentes antimicrobial, patientes esseva generalmente admittite con acute infectiones staphylococcal que illes habeva acquirite foras del hospital. In le era presente, serie infectiones staphylococcal occurre in patientes de etates plus avantiate qui se trova jam hospitalisate con altere serie morbos como per exemplo dermatitis exfoliative, diabete, malignitate, o complexe problemas operatori. In iste gruppo le mortalitate ha essite considerabile.

Ben que racias staphylococcal con resistentia contra agentes antimicrobial representa un serie problema, resistentia a medication per se non esseva generalmente le causa del non-successo therapeutic, e le majoritate del recentemente isolate staphylococcos se ha monstrate susceptibile al effectos de un del nove agentes antimicrobial. In le majoritate del casos, le subjacente morbo primari esseva le factor decisive in le resultato final, e le infection staphylococcal occurreva como evento terminal al hospital.

Il pare pauco probabile que nove agentes antimicrobial va alterar de maniera significative le mortalitate ab infectiones staphylococcal post que istos se ha establite in patientes con serie altere morbos. Il existe certe indicationes que le incidentia de infectiones staphylococcal intra le hospital pote esser reducite per un plus judiciose utilisation del agentes antimicrobial, specialmente pro objectivos prophylactic, e per le adoption de mesuras destinate a prevenir le translation de micro-organismos ab le personal al patientes.

Methodos destinate a prevenir infectiones staphylococcal in patientes qui es seriemente malade debe esser definite plus nettemente. Progresso in iste direction pare promitter plus que le uso de nove agentes antistaphylococcal pro le reduction del incidentia de morbo staphylococcal.

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THE DIAGNOSTIC, PROGNOSTIC AND EPIDEMIOLOGIC SIGNIFICANCE OF SERUM GLUTAMIC OXALOACETIC TRANSAMINASE (SGO-T) ALTERATIONS IN ACUTE HEPATITIS *

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Introduction

Glutamic oxaloacetic transaminase (GO-T) is widely distributed in animal and human tissues. Its greatest activity has been found in homogenates of heart muscle, skeletal muscle, brain, liver and kidney, the relative activities varying in different species (table 1). This enzyme activity has been found in all animal and human sera tested, and the activities are comparable whether determined chromatographically,[1] spectrophotometrically [2] or colorimetrically [3] (figure 1). It has been demonstrated that serum

Table 1

Distribution of Glutamic Oxaloacetic Transaminase Activity in Tissue Homogenates

Tissue	Dog	Human
	units/gm. wet tissue	
Heart	320,000	156,000
Liver	200,000	142,000
Skeletal muscle	210,000	99,000
Kidney	43,000	91,000
Serum	20	28

glutamic oxaloacetic transaminase (SGO-T) activity increases two to 20 times following acute myocardial infarction,[4] and may rise to 20 to 500 times normal in acute hepatitis due to toxic or infectious agents.[5]

This report will describe the SGO-T activity alterations in acute hepatitis, and discuss the usefulness of this procedure in the diagnosis and management of hepatitis and in following the epidemiologic course of infectious hepatitis.

Methods and Material

Serum glutamic oxaloacetic transaminase was measured by the spectrophotometric method previously described.[2] The mean activity of adult human serum is 22.1 units, with a standard deviation of 6.8. The normal

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range of activity for adult human sera is five to 40 units, determined at a temperature of 20 to 23° C. SGO-T is not elevated in patients with infectious, neoplastic, degenerative, reactive, allergic or congenital disease states unless evidence of acute damage to liver, heart or skeletal muscle is present. It has been postulated that the probable mechanism for increase in SGO-T activity following acute myocardial infarction is the release of the enzyme from damaged cells into the blood stream.[6] A metabolic or excretory aberration may also contribute to SGO-T elevation during liver cell damage.[7, 8]

Patients with infectious hepatitis, homologous serum hepatitis and toxic hepatitis were carefully followed in the hospital over a three-week to three-

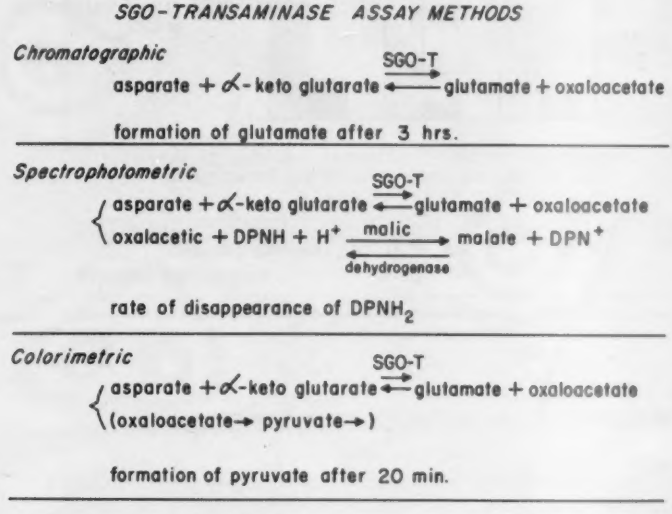


FIG. 1. Chemical reactions involved in the measurement of SGO-T by various technics.

month period. SGO-T activity was determined at frequent intervals, and the following liver function tests were also obtained: serum bilirubin, alkaline phosphatase, total protein and A/G ratio, cephalin flocculation, thymol turbidity, urinary bile and urobilinogen and, in some instances, Bromsulphalein retention. Similar studies were done on patients with other types of hepatic and biliary tract disease and will be outlined as they relate to the differential diagnosis of hepatitis.

At an institution for mental defectives, 14 patients with infectious hepatitis were studied. The individuals in this institution live in communal buildings of various capacities. In the case of each patient who developed and was hospitalized for infectious hepatitis, all of the inmates living in the building in which the case of infectious hepatitis developed were exam-

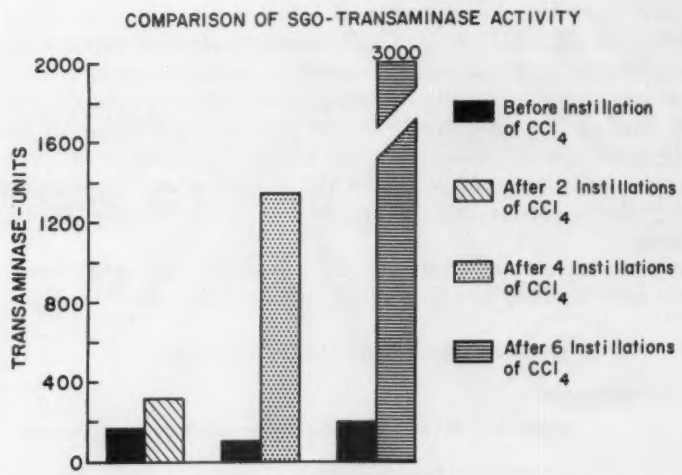


FIG. 2. Comparison of the SGO-T alterations following the instillation into the rat of various amounts of carbon tetrachloride.

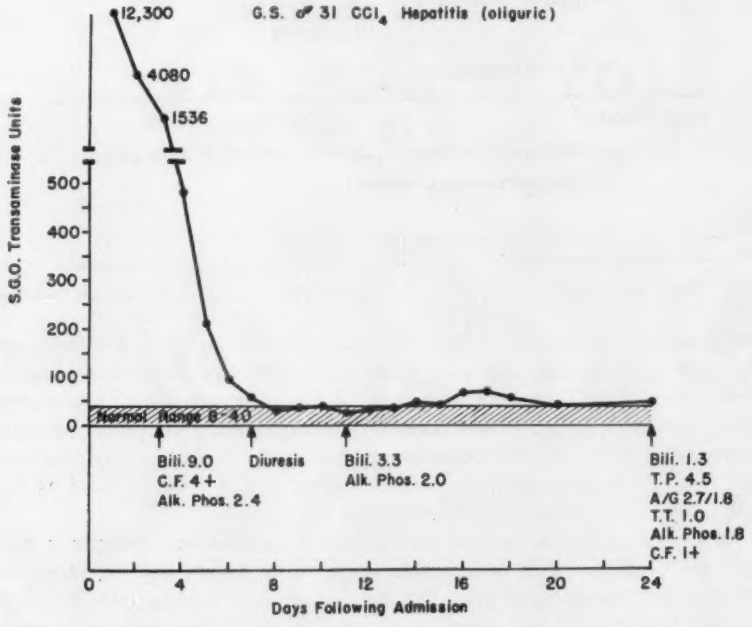


FIG. 3. SGO-T alterations and liver function tests in a patient with toxic hepatitis due to accidental exposure to carbon tetrachloride.

ined and the SGO-T was determined for each inmate. When a contact individual demonstrated an abnormal SGO-T activity, the inmate was re-examined weekly and the SGO-T activity was determined weekly until it returned to normal or until the patient developed symptoms and was hospitalized for infectious hepatitis. Simultaneously with the determination of SGO-T, serum bilirubin and thymol turbidity were measured. Occasionally, cephalin flocculation and Bromsulphalein retention were ascertained. Those individuals hospitalized with clinical infectious hepatitis had SGO-T determinations three or more times a week, as well as a battery of conventional liver function tests.

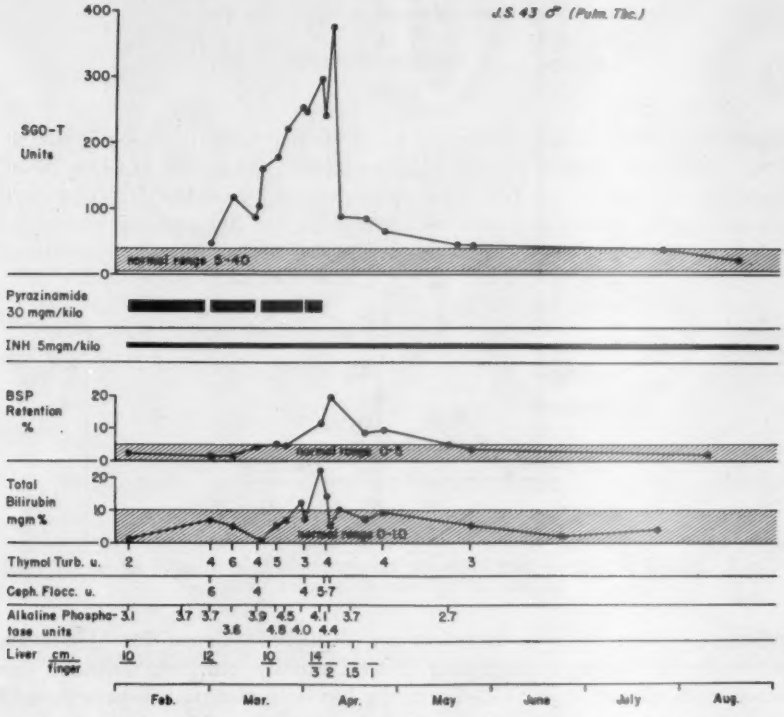


FIG. 4. Comparison of the serial changes in SGO-T activity with liver function tests in a patient with toxic hepatitis due to pyrazinamide.

RESULTS

Toxic Hepatitis: As previously reported, SGO-T is a sensitive index of hepatocellular injury.[7] With the use of rats in which toxic hepatitis was produced with carbon tetrachloride, there appeared to be a proportional relationship between the quantitative increase in SGO-T and the severity

of liver cell damage which, in turn, was proportional to the amount of carbon tetrachloride administered (figure 2). Acute toxic hepatitis caused by accidental exposure to carbon tetrachloride results in a striking elevation of SGO-T activity, which rapidly falls toward the normal range when exposure to the hepatotoxin is terminated (figure 3). The toxic hepatitis resulting from drugs likewise causes a rise in SGO-T, but the elevation is smaller than that seen after exposure to carbon tetrachloride. If the hepatotoxic drug is continued there is a progressive rise in SGO-T. It appears that the sensitivity of SGO-T in reflecting hepatocellular injury results in SGO-T activity above the normal range before the thymol turbidity, bili-

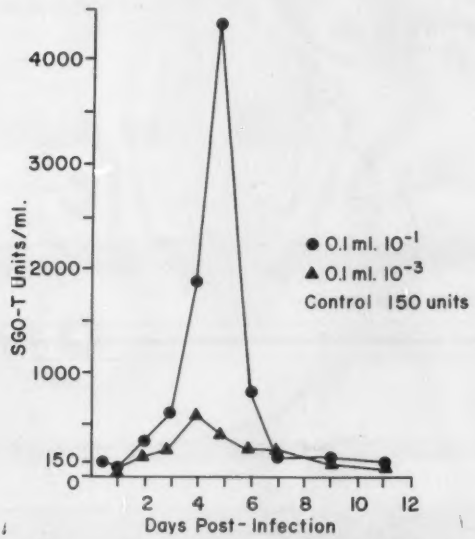


FIG. 5. SGO-T activity in mice following intraperitoneal inoculation of 0.1 ml. 10^{-1} and 0.1 ml. 10^{-3} dilution of hepatitis virus.

rubin or Bromsulphalein excretion are disturbed (figure 4). Upon the withdrawal of the hepatotoxic drug, SGO-T rapidly returns to normal. This sequence of alteration in SGO-T activity has been observed in patients with toxic hepatitis from Thorazine, azoserine, pyrazinamide, cinchophen and massive doses of aspirin. In this type of toxic hepatitis, the SGO-T activity, although not rising to such heights as in carbon tetrachloride poisoning, shows the same serial changes.

Infectious Hepatitis and Homologous Serum Hepatitis: A previous report has indicated that experimental infectious mouse hepatitis is associated with an increase in SGO-T, and that a relationship appears to exist between the rise in SGO-T activity and (a) the size of the virus inoculum (figure 5),

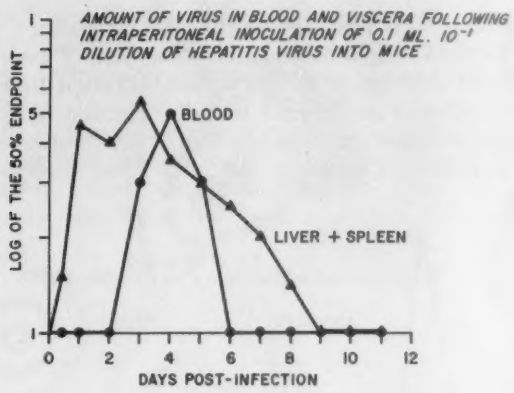


FIG. 6.

(b) the blood virus titer (figure 6), and (c) the degree of liver necrosis.[9] In 40 patients with infectious hepatitis, a rise in SGO-T reaching a peak from 400 to 2,500 units has been observed.[5] Figure 7 illustrates the same laboratory findings and SGO-T alterations seen in a patient with infectious hepatitis, and typifies the observations made during the clinical course of

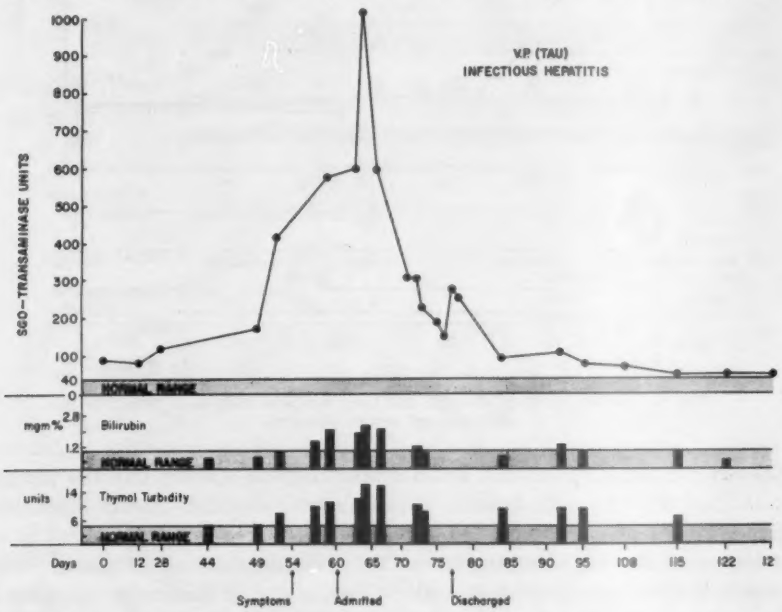


FIG. 7. Serial SGO-T, serum bilirubin and thymol turbidity alterations in a patient with acute infectious hepatitis. See text for explanation.

most of the patients with infectious hepatitis. This patient (V. P.) had had contact with an individual with hepatitis. The SGO-T activity was abnormal on the initial observation in this patient, although Bromsulphalein retention, serum bilirubin and thymol turbidity reaction were normal. The patient was asymptomatic until the fifty-fourth day of observation, at which time nausea and anorexia appeared; the SGO-T had risen to 400 units and

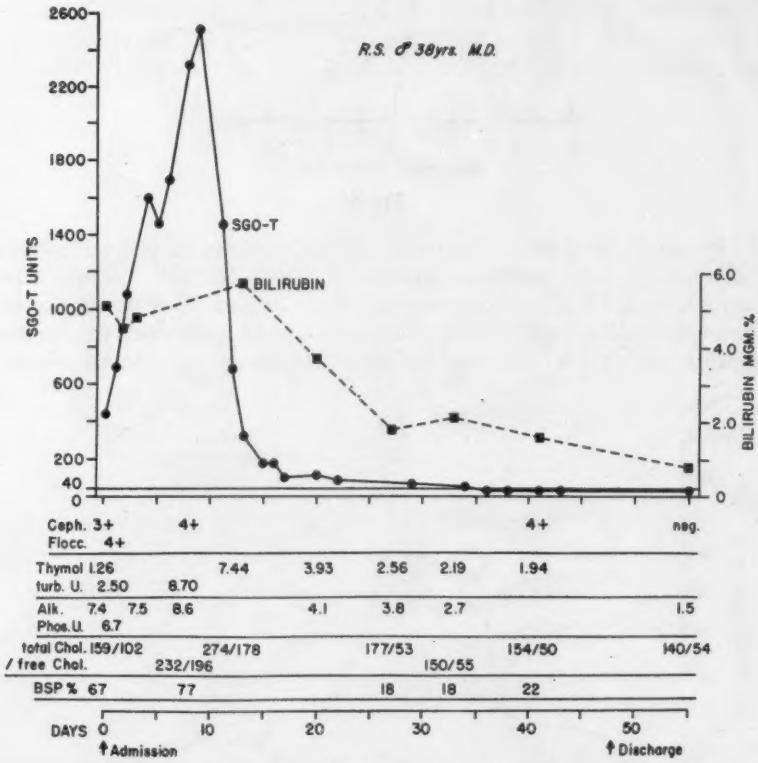


FIG. 8. SGO-T activity changes and liver function tests in a patient with homologous serum hepatitis.

the thymol turbidity reached seven units. By the sixtieth day the patient was clinically ill, with icterus, hepatomegaly, elevated thymol turbidity, hyperbilirubinemia and an SGO-T of 560 units. He was hospitalized from the sixtieth day to the seventy-seventh day of observation. Although nonicteric but still complaining of malaise on the day of discharge, the patient was observed to have a secondary rise in SGO-T activity associated with the resumption of his usual activities.

When SGO-T activity was increasing progressively the patient subjectively seemed sickest, as adjudged by the presence of malaise, anorexia, nausea, vomiting, fever and hepatic tenderness. These symptoms and signs reached a maximum at the time that the SGO-T reached a peak. With the fall in SGO-T, the patients were noted to improve subjectively and objectively, although the jaundice and/or hyperbilirubinemia may not begin to recede for several days. It appears that the sicker the patient with infectious hepatitis, the higher the peak SGO-T. A similar course of

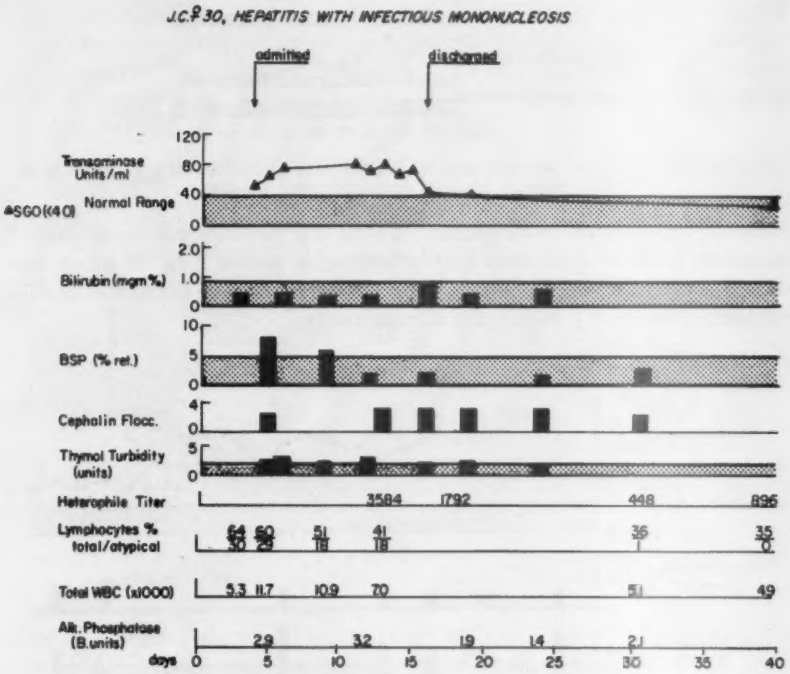


FIG. 9. SGO-T alterations and other laboratory data in a patient with infectious mononucleosis complicated by hepatitis.

events and laboratory alterations have been noted in 20 patients with homologous serum hepatitis which affects SGO-T activity in a manner indistinguishable from that described for infectious hepatitis (figure 8).

When infectious mononucleosis is complicated by hepatic involvement, SGO-T activity is increased above the normal range.[10] Figure 9 illustrates the changes in SGO-T activity observed in a patient (J. C.) with hepatitis complicating acute infectious mononucleosis. The laboratory finding and SGO-T alterations depicted are typical of six patients with infectious mono-

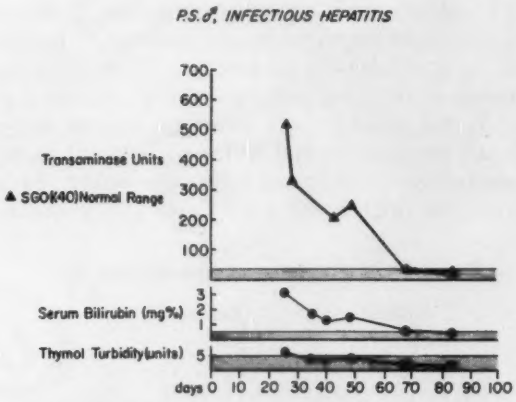


FIG. 10. SGO-T, serum bilirubin and thymol turbidity alterations in a patient during the recovery phase of acute infectious hepatitis.

nucleosis complicated by hepatitis. These six patients exhibited SGO-T elevations of 80 to 300 units over a four-week period. In 10 other individuals with infectious mononucleosis not affecting the liver, the SGO-T remained consistently within the normal range.

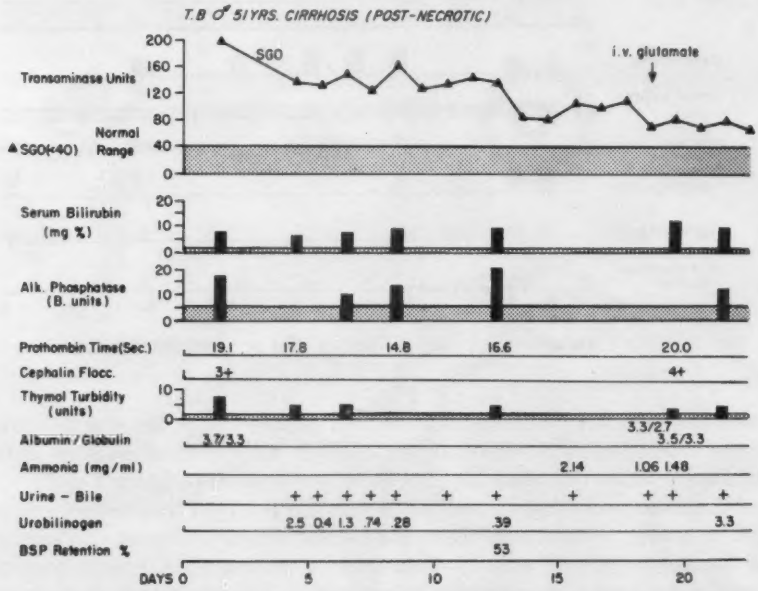


FIG. 11. SGO-T alterations and other laboratory data in a patient who succumbed to postnecrotic cirrhosis.

Although acute hepatitis is associated with a gradual increase followed by a gradual decrease in SGO-T activity, many hospitalized patients are seen at the peak of or during the recovery phase of the acute disease. Figure 10 depicts the characteristic SGO-T changes seen in an individual typical of this group of patients with acute hepatitis.

Other Types of Hepatic Disease: Measurement of the SGO-T activity during the acute phase of hepatitis, whatever its course, usually permits differentiation of this cause of jaundice from that due to cirrhosis, extrahepatic obstruction of the biliary tract, hepatoma, liver metastases and hemolysis. Cirrhosis, when compensated, is associated with normal SGO-T. When decompensated or active, as adjudged by the presence of jaundice, abdominal pain, ascites and edema, cirrhosis is associated with elevated SGO-T varying from 40 to 300 units, with daily fluctuations about a mean

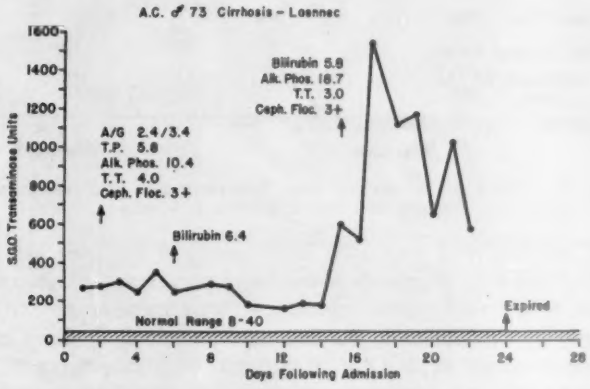


FIG. 12. SGO-T alterations and liver function tests in a patient with decompensated Laennec's cirrhosis on which acute hepatitis was superimposed.

above the normal range. Figure 11 shows the SGO-T alterations in a patient with active postnecrotic cirrhosis. The superimposition of acute hepatitis on a cirrhotic liver results in alterations of SGO-T characteristic of those described for hepatitis. Figure 12 depicts the SGO-T alterations in a cirrhotic patient who developed hepatitis.

Extrahepatic biliary obstructive jaundice is characterized by increments in SGO-T activity of approximately 100 to 300 units. The enzyme level rapidly falls to normal following relief of the biliary obstruction (figure 13); the SGO-T activity usually returns to normal within two to eight days, while the alkaline phosphatase has remained elevated for several days longer in several of the patients we have followed.

In 75 of 100 patients with primary hepatoma or hepatic metastases, SGO-T activity was elevated from 45 to 250 units. The alterations of

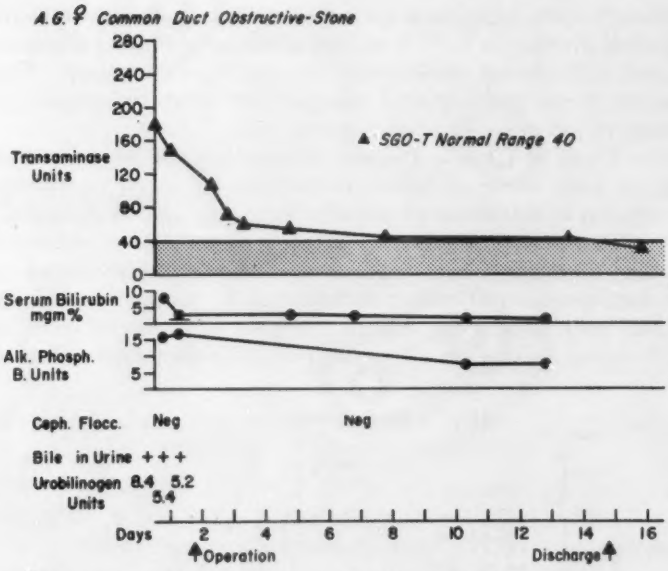


FIG. 13. SGO-T alterations and other laboratory data in a patient with common duct obstruction due to stone.

SGO-T in patients with neoplastic involvement of the liver are dependent upon the size and rate of growth of the neoplastic areas. Although alkaline phosphatase is altered by both hepatic and bony metastases, SGO-T is influenced only by metastases to the liver and not at all by bony metastases. Serial determinations of SGO-T in patients with carcinoma of the liver reveal variable elevations from day to day of relatively lower magnitude of serum enzyme activity.

Acute myocardial infarction, surgical trauma to skeletal muscle, and any process associated with acute injury to skeletal muscle or heart muscle may result in increased SGO-T activity. These clinical situations present little or no confusion diagnostically, inasmuch as they present in different clinical settings and are reflected by SGO-T alterations of significantly different magnitudes and serial changes.

PROGNOSIS

The natural uncomplicated course of infectious hepatitis is associated with a gradual rise in SGO-T activity to a peak, followed by a gradual decrease in serum enzyme activity toward the normal range during the recovery phase. When infections or other complications occur during the course of hepatitis, the added stress tends to influence the hepatitis, and this is reflected in a secondary, superimposed rise in SGO-T activity (figure 14).

Ambulation during recovery from infectious hepatitis is sometimes associated with a small secondary rise in SGO-T. If the rise following ambulation is 50 or more units, return to rest discipline appears advisable, and SGO-T usually resumes its return toward normal. Figure 15 shows the SGO-T alterations in a patient (N. P.) with homologous serum hepatitis. Premature ambulation was associated with a rise of SGO-T

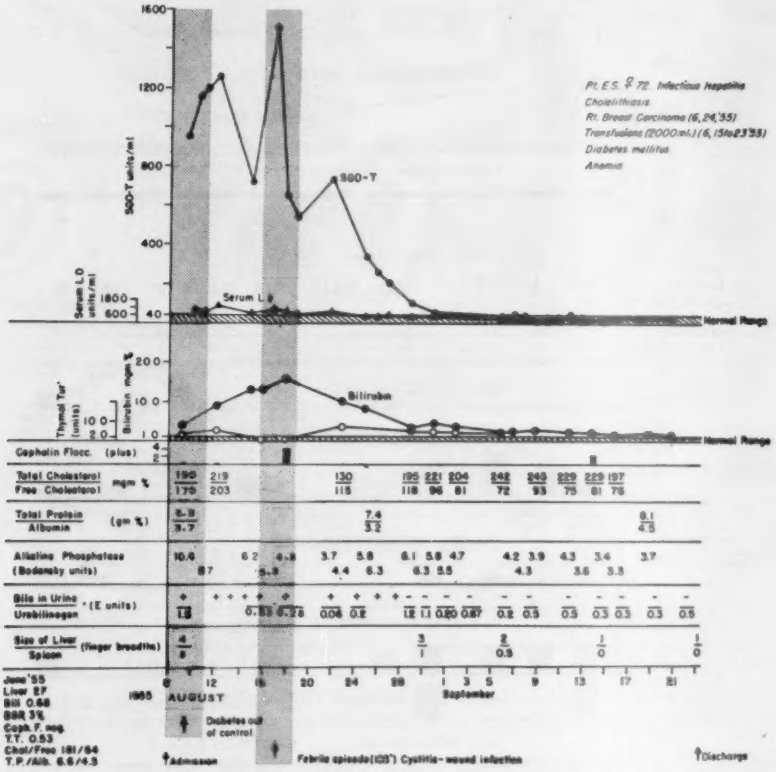


FIG. 14. SGO-T alterations associated with acute hepatitis in a patient who developed an acute urinary tract infection. The added stress of the genitourinary tract infection resulted in a secondary rise in SGO-T activity.

of 60 units on the twentieth day of the hospital course, and there was reappearance of malaise, hepatic tenderness and right upper quadrant pain. Resumption of rest for a two-week period resulted in disappearance of symptoms and a return of SGO-T to normal range. A similar set of events occurred in a previously cited patient whose SGO-T alterations are shown in figure 7.

Relapses of infectious hepatitis are associated with secondary rises in SGO-T activity. Unresolving hepatitis, because of uncontrollable disease or because of inadequate or ineffective treatment, is associated with a persistently elevated SGO-T. Figure 16 depicts the SGO-T activity in a

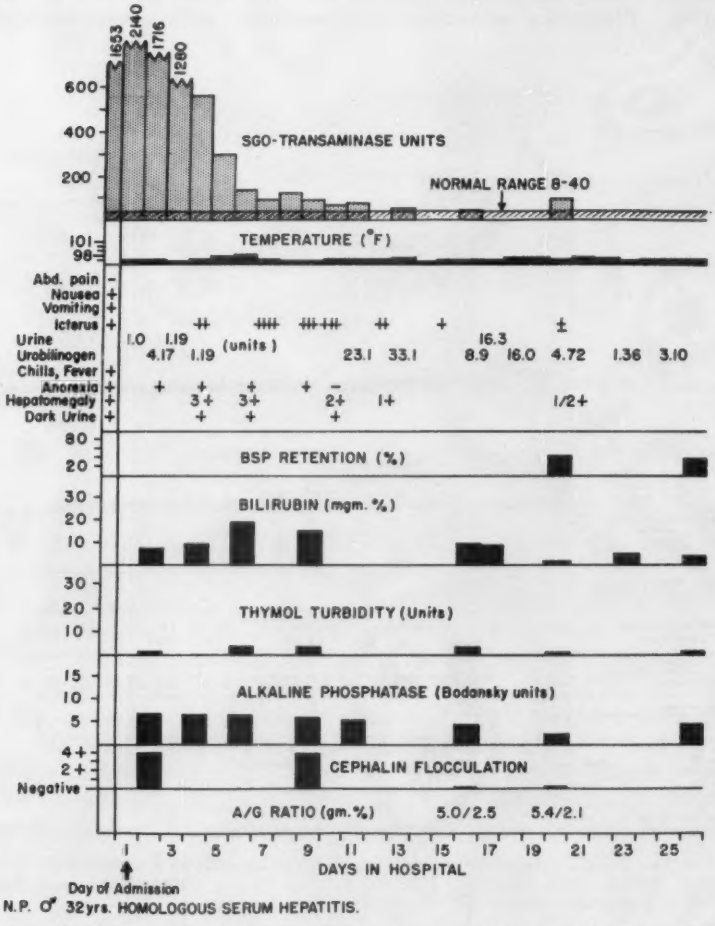


FIG. 15. SGO-T alterations and other laboratory data in a patient with homologous serum hepatitis. Ambulation on the twentieth day resulted in a rise in SGO-T activity.

patient who, one year previously, had had infectious hepatitis which was inadequately treated. When seen, she had jaundice, hepatomegaly and a continuing elevation of SGO-T activity. Aspiration biopsy of the liver revealed chronic hepatitis with postnecrotic cirrhosis. Study of serial alter-

ations of SGO-T gives a clue as to the development of chronic hepatitis or relapsing hepatitis. The failure of SGO-T activity to return to the normal range suggests the development of chronic hepatitis and/or post-infectious cirrhosis. The serial alterations of SGO-T in the course of infectious hepatitis follow a characterized pattern; deviations from this usual course of enzyme alterations suggest associated complication, relapse and/or smoldering infectious hepatitis.

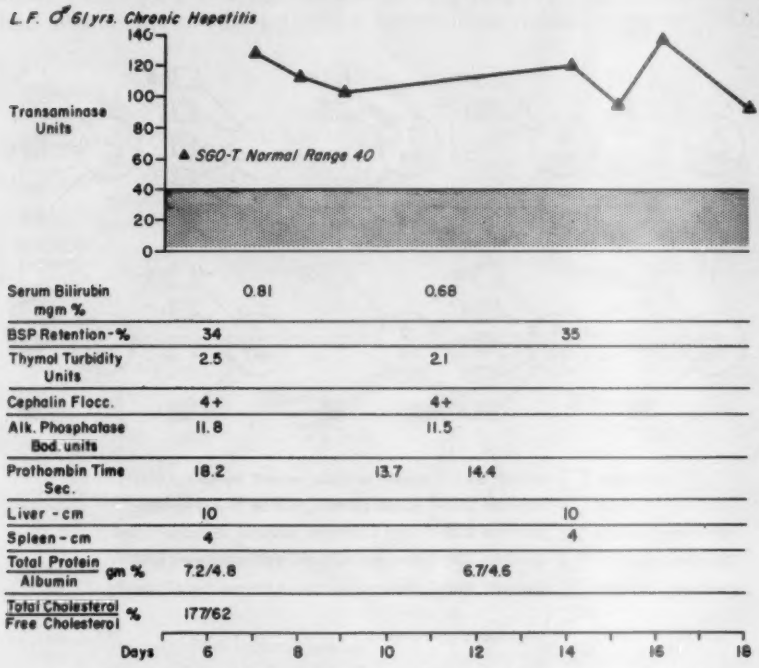


FIG. 16. Alterations in SGO-T activity with other laboratory and clinical data in a patient with chronic hepatitis.

EPIDEMIOLOGIC CONSIDERATIONS

The sensitivity of SGO-T activity in detecting acute hepatitis suggested its use in the study of asymptomatic and non-icteric symptomatic individuals during the course of a high endemic incidence of infectious hepatitis in a closed institutional environment. It was the purpose of this survey to ascertain whether asymptomatic individuals in communal contact with patients hospitalized for infectious hepatitis had laboratory evidences of acute hepatitis which were unrecognized clinically.

In a closed institutional environment in which mentally defective individuals lived in cottages, a survey was made of the alterations in SGO-T

activity in individuals who had contact with inmates hospitalized for infectious hepatitis. When a patient with infectious hepatitis was recognized, those individuals living in the same cottage were examined and SGO-T, serum bilirubin and thymol turbidity were determined once weekly over a three- to nine-month period of observation. Figure 17 diagrammatically depicts the observations in nine cottages, one of which had a case of acute infection on two occasions four months apart. The contact individuals fell into five groups: (a) asymptomatic individuals with persistently normal SGO-T, serum bilirubin and thymol turbidity; (b) asymptomatic indi-

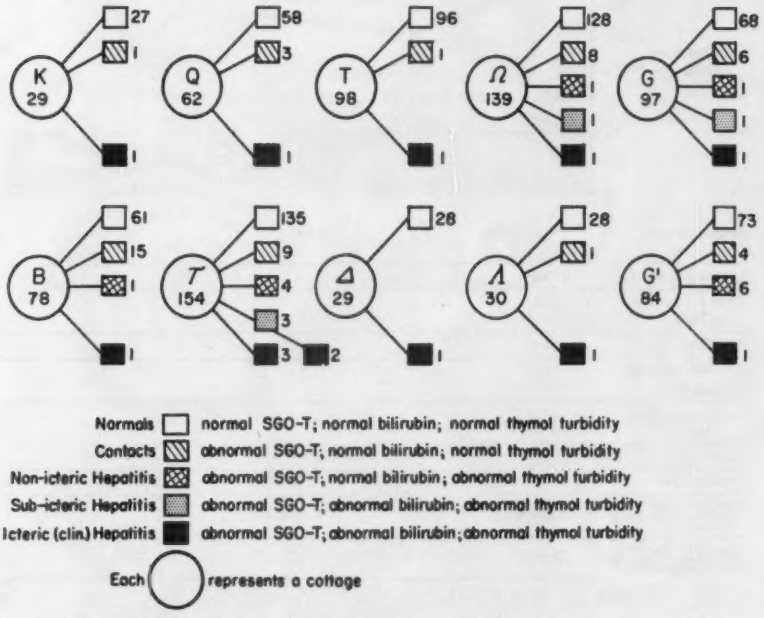


FIG. 17. The epidemiologic incidence of subclinical and clinical infectious hepatitis in a closed institutional environment. See text for discussion.

viduals with transiently abnormal SGO-T (less than 100 units), with normal serum bilirubin and thymol turbidity; (c) asymptomatic individuals with normal serum bilirubin and abnormal thymol turbidity; (d) symptomatic individuals with abnormal SGO-T (less than 350 units), with hyperbilirubinemia and abnormal thymol turbidity; (e) symptomatic individuals with clinical icteric hepatitis with abnormal SGO-T (greater than 400 units), with hyperbilirubinemia and abnormal thymol turbidity. These individuals were categorized respectively as (a) normals, (b) contacts, (c) non-icteric hepatitis contacts, and (d) sub-icteric hepatitis contacts. The final group of inmates consisted of those individuals who developed icteric

clinical infectious hepatitis which required hospitalization. Figure 18 shows the SGO-T alterations, serum bilirubin and thymol turbidity in individuals in four of the five categories; a normal individual typically shows normal values of SGO-T, serum bilirubin and thymol turbidity.

Cottage Tau exemplifies the epidemiologic behavior of acute infectious hepatitis in a communal institutional environment. In cottage Tau, which

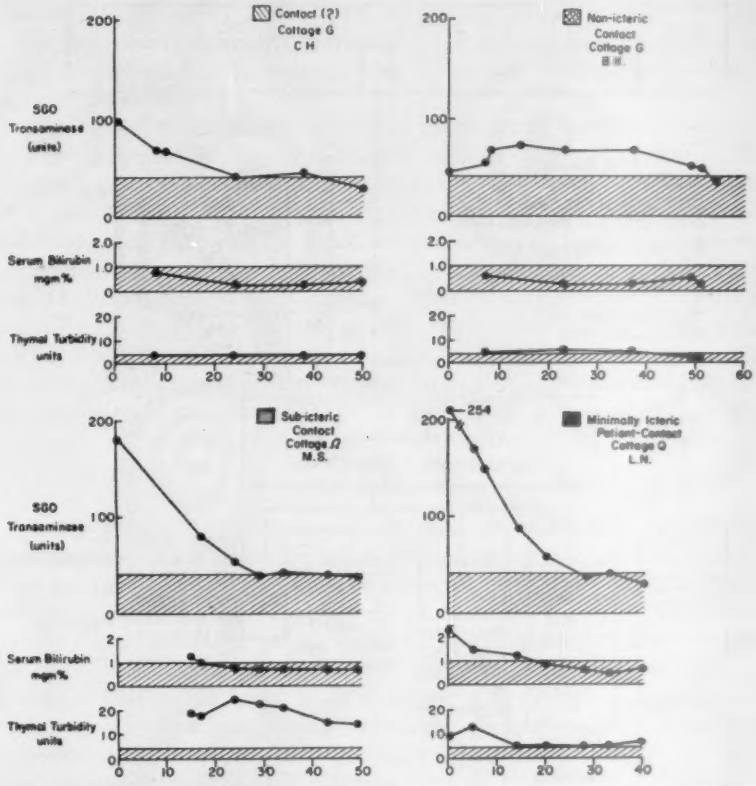


FIG. 18. Comparison of the SGO-T alterations observed in patients with subclinical and clinical acute infectious hepatitis. See text for discussion.

housed 154 inmates, three inmates developed infectious hepatitis for which they were immediately hospitalized. At the same time that the three patients with infectious hepatitis were hospitalized, venous sera were drawn once weekly from the remaining 151 occupants. Sixteen inmates had elevation of SGO-T activity above 40 units during the first week of the study. The remaining 133 had persistently normal SGO-T activity during the remaining three months of observation (figure 19). The 16 patients

with increased SGO-T activity were divided into three groups. Nine had SGO-T activities above 40 but less than 100 units; all had normal liver function tests, and in all the SGO-T activity fell to normal in less than 28 days. The second group of four had SGO-T activity varying from 100 units to 350 units; the serum bilirubin in all was normal, and the thymol

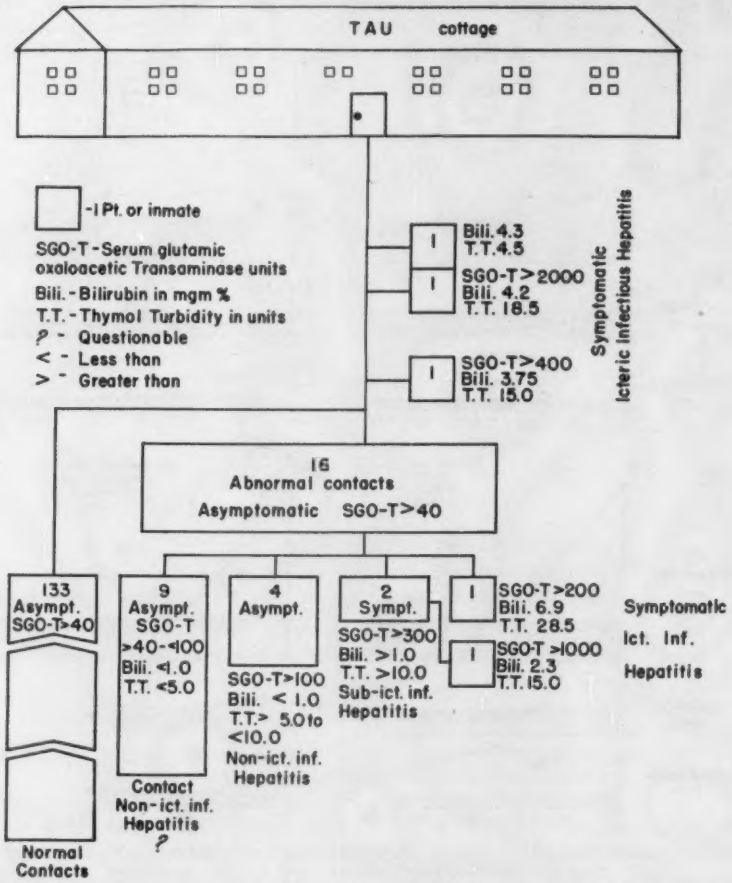


FIG. 19. Diagram of the SGO-T alterations observed in a systemic study of contacts in cottage Tau in which three inmates were hospitalized with infectious hepatitis. See text for discussion.

turbidity was above five but less than 10 units. The peak SGO-T activity of the remaining three inmates (two of whom were hospitalized) ranged from 390 to 1,800 units; the serum bilirubin was 2.3, 4.5 and 6.9 mg.%, and the thymol turbidity was 18.0, 20.0 and 26.5 units, respectively. None of the individuals with normal SGO-T activity developed any symptoms or

signs of hepatitis over the six-month period of study. One individual followed over a 73-day period was seen to pass successively from group one to group three, first having an SGO-T activity of 76 which rose to 168 in 30 days, and on the sixty-fifth day was 1,008, when the bilirubin was 2.3 mg.% and the thymol turbidity 15.0 units.

These and other epidemiologic observations suggest that asymptomatic non-icteric and subicteric individuals may possibly communicate the disease without themselves being recognized as having acute hepatitis. It would appear that the viremia and/or viruchezia in asymptomatic nonicteric and subicteric individuals in contact with infectious hepatitis may serve to transmit the disease.

SGO-T elevations above the normal range readily permit the detection of acute hepatitis in the asymptomatic and/or prodromal phase. This would suggest that measurement of SGO-T of all contacts during an epidemic would permit differentiating those individuals who may develop nonicteric, subicteric and/or frank icteric infectious hepatitis from those individuals who are to remain well. The former group could then be prophylactically treated with immune globulin without unnecessarily administering this material to the larger group of individuals with normal SGO-T who are not potential candidates for subclinical and/or clinical acute hepatitis. The suggestion that during an epidemic of infectious hepatitis individuals with abnormal SGO-T be isolated in order to stop the dissemination of the disease has as yet to be tested.

Conclusions

Serum glutamic oxaloacetic transaminase alteration is a sensitive and roughly proportional index of hepatocellular injury during acute hepatitis of various etiologic types. Acute and chronic hepatic disease is associated with quantitative and serial elevations of SGO-T activity which are sufficiently characteristic to permit diagnostic differentiation. The subjective and objective clinical course of patients with acute hepatitis appears to be accurately reflected in serial SGO-T alterations. Relapses, exacerbations, chronicity, premature ambulation and unrelated superimposed complications in patients with acute hepatitis are usually evidenced by variations from the usual pattern of serial SGO-T changes.

The SGO-T changes observed in the prodromal phase of hepatitis and in individuals with asymptomatic and/or subicteric types of acute hepatitis permit a better understanding of the epidemiologic course of this disease. The epidemiologic observations presented suggest additional methods for the management of infectious hepatitis in endemic and epidemic situations.

Summario in Interlingua

Transaminase glutamic oxalacetic (T-GO) es extensemente distribuite in histos animal e human. Su plus grande activitate ha essite constatate in homogenatos de musculo cardiac, musculo skeletic, cerebro, hepate, e ren. Le grados relative del

activitate in le varie histos varia ab un specie al altere. Activitate de T-GO ha essite trovate in omne seros animal e human examinate. Su grados es comparabile quando illos es determinate chromatographicamente, spectrophotometricamente, o colorimetricamente. Ha essite demonstrate que le activitate de T-GO del sero se augmenta duo a 20 vices post acute infarcimento myocardial e que illo pote attinger nivellos de inter 20 e 500 vices le norma in hepatitis acute causate per agentes toxic o infectiose.

Le presente reporto describe alterationes del activitate de T-GO seral in hepatitis acute e discute le utilitate del determination de iste activitate enzymatic in le diagnose e le tractamento de hepatitis e in le observation del curso epidemiologic de hepatitis infectiose.

Alterationes del activitate de T-GO seral es un sensibile indice, plus o minus directemente proportional, del lesion hepatocellular occurrente durante hepatitis acute de varie typos etiologic. Acute e chronic morbo hepatitic es associate con elevationes quantitative e serial del activitate de T-GO seral, le quales es sufficientemente characteristic pro supportar le differentiation diagnostic. If pare que le objective e le subjective curso de patientes con hepatitis acute es accuratemente reflectite in serial alterationes del activitate de T-GO seral. Recidivas, exacerbationes, chronicitate, ambulation prematur, e non-affin complicationes superimponite in patientes con hepatitis acute es usualmente evidentiate in deviationes ab le curso typic del alterationes in le activitate de T-GO seral.

Le alterationes del activitate de T-GO seral observate in le phase prodromic de hepatitis e in individuos con typos asymptomatic e/o subicteric de hepatitis acute permitte un meliorate comprension del curso epidemiologic de iste morbo. Le observationes epidemiologic hic presentate suggere le disveloppamento de methodos additional pro le tractamento de hepatitis infectiose in situationes endemic e epidemic.

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SERUM GLUTAMIC PYRUVIC TRANSAMINASE (SGP-T) IN HEPATIC DISEASE: A PRELIMINARY REPORT * †

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Introduction

Significant and characteristic alterations in the activity of serum glutamic oxaloacetic (SGO-T) have been shown to follow acute heart muscle and liver cell injury and to provide a rough index of the degree of such damage.[1, 2] The activity of glutamic oxaloacetic transaminase (GO-T) and that of glutamic pyruvic transaminase (GP-T) in homogenates of various human tissues are compared in table 1. The relative concentration of GP-T in liver as compared with heart tissue and skeletal muscle is proportionately greater than that of GO-T. This observation suggested that serum glutamic pyruvic transaminase (SGP-T) might be a more specific index of liver cell damage than SGO-T because of the more selective concentration of GP-T in liver tissue. Conversely, since the activity of GP-T is low in heart muscle, myocardial necrosis might be followed by small or insignificant increases in SGP-T, and SGP-T might therefore be expected to provide a more specific index of liver cell damage.

Method of Study

SGP-T activity has been measured chromatographically,[3] spectrophotometrically [4] and colorimetrically.[5] In this study a rapid and simple spectrophotometric technic was employed to determine SGP-T activity. The transamination reaction (Reaction 1) is coupled to the reduction of pyruvate to lactate by reduced diphosphopyridine nucleotide (DPNH) in the presence of added excess of purified lactic dehydrogenase (Reaction 2).

$$\alpha\text{-keto glutarate} + \text{1-alanine} \xrightarrow[\text{SGP-T}]{} \text{glutamate} + \text{pyruvate} \quad \text{(Reaction 1)}$$

$$\text{pyruvate} + \text{DPNH} \xrightarrow[\text{lactic dehydrogenase}]{} \text{lactate} + \text{DPN} \quad \text{(Reaction 2)}$$

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TABLE 1

Comparison of Glutamic Oxaloacetic Transaminase and Glutamic Pyruvic Transaminase In Normal Adult Tissue Homogenates

Tissue	GO-T	GP-T
	Units/gm. wet tissue	
Heart	156,000	7,100
Liver	142,000	44,000
Skeletal muscle	99,000	4,800
Kidney	91,000	19,000
Pancreas	28,000	2,000
Spleen	14,000	1,200
Lung	10,000	700
Serum	20	16

Oxidation of DPNH, and thereby the transamination reaction, is followed by measuring the decrease in light absorption at wave length 340 mu at which reduced diphosphopyridine nucleotide has an absorption peak. The optical density at wave length 340 mu was followed for five minutes and the rate of decrease in optical density taken as measure of the glutamic pyruvic transaminase activity of the serum. The reaction was followed in a Beckman DU spectrophotometer at room temperature (23° C.). Serum activity is expressed in units/ml./minute. One unit equals a decrease in optical density of 0.001 mu under the conditions described.

RESULTS

Glutamic pyruvic transaminase was measured at 23° C. in sera of 260 normal humans and the activities had a mean value of 16 ± 9 units/ml./minute. When the mean value of SGP-T activity is converted to micromoles/ml./hour, the values fall within the range of 0.23 to 0.82 micromole/ml./hour found by quantitative paper chromatographic assay previously reported.[3]

In the absence of liver disease, SGP-T activity has not been observed to be significantly increased by the presence of infectious, neoplastic, reactive, degenerative, congenital or allergic disease states. The SGP-T failed to increase significantly following necrosis resulting from acute myocardial infarction in eight of nine patients (table 2). Figure 1 depicts serial SGP-T alterations in a 63 year old female who incurred an acute transmural

TABLE 2

Comparison of Peak SGO-T and SGP-T in Nine Patients With Acute Transmural Myocardial Infarction

Case No.	Peak SGO-T	Peak SGP-T
1	250	70
2	224	32
3	168	26
4	150	30
5	80	38
6	70	25
7	66	23
8	61	18
9	54	17

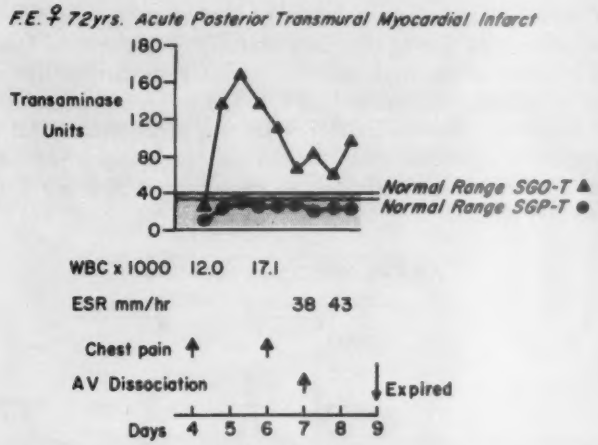


FIG. 1. Compares the SGO-T and SGP-T activity following an acute posterior transmural myocardial infarction.

posterior myocardial infarction; the changes in SGO-T are in sharp contrast to the normal SGP-T activity. In one patient (S. G.), an acute posterior myocardial infarct was associated with a rise in SGO-T to 260 units and SGP-T to 70. The SGP-T returned to normal in 48 hours, whereas the SGO-T remained elevated for five days. The lack of significant alterations

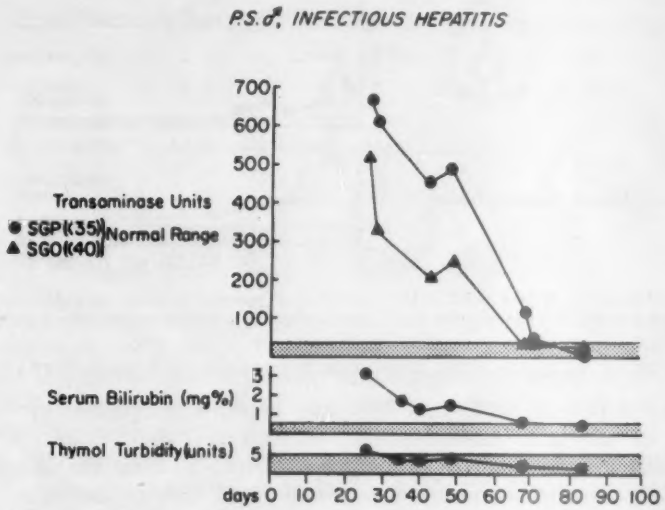


FIG. 2. Shows the variations in SGP-T and SGO-T activity, in serum bilirubin and in the thymol turbidity reaction over an 83 day period in a patient with acute hepatitis.

in SGP-T activity following most instances of acute myocardial infarction is probably accounted for by the fact that GP-T activity is low in heart muscle, in contrast to the high activity of GO-T in cardiac tissue. When the infarct is sizable, the amount of GP-T liberated appears to be great enough to transiently elevate SGP-T. During acute myocardial infarction SGP-T appears to be altered above the normal range only when the resulting myocardial necrosis is great enough to cause a rise in SGO-T of greater than 150 to 200 units.

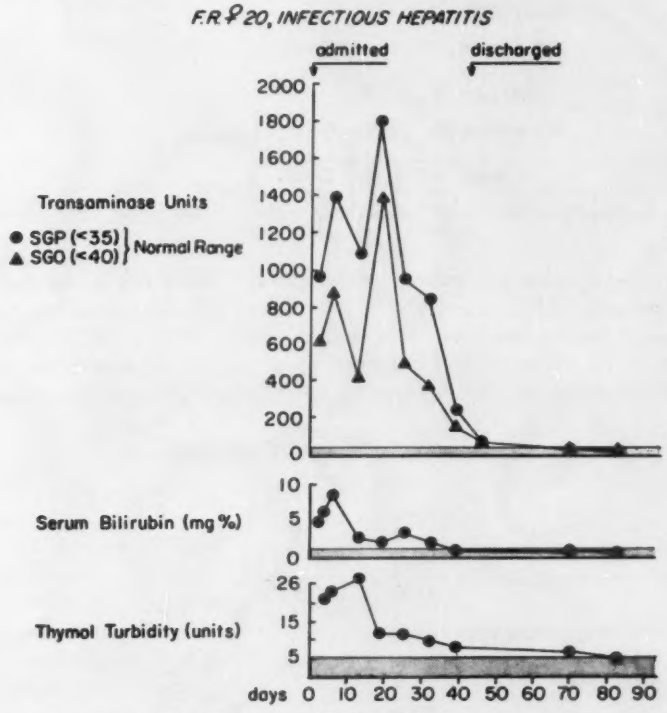


FIG. 3. Shows the variations in SGP-T and SGO-T activity, in serum bilirubin and in the thymol turbidity reaction over an 83 day period in a patient with acute hepatitis.

ACUTE INFECTIOUS HEPATITIS AND HOMOLOGOUS SERUM HEPATITIS

Twelve patients with viral infectious hepatitis complained in varying degree of anorexia, nausea, emesis, pruritus and dark urine. All had hepatomegaly and jaundice of different degree; in three the spleen was palpable. Hospital admission was within seven days of the onset of the illness in four patients, and approximately 21 days in eight patients. Figure 2 shows the levels of SGO-T, SGP-T, serum bilirubin and thymol turbidity

in an 83 day period in a 30 year old male with infectious hepatitis. Seven days after admission and after 14 symptom days the SGP-T activity was 670 units, as contrasted with 520 units for SGO-T. The patient was prematurely discharged from the hospital, and following his ambulation there was a secondary rise in both SGP-T and SGO-T activities, which fell to normal within the next 30 days. Figure 3 illustrates similar data in a 20 year old female (F. R.) with infectious hepatitis who experienced a more symptomatically severe form of the disease. She was admitted to the hospital 10

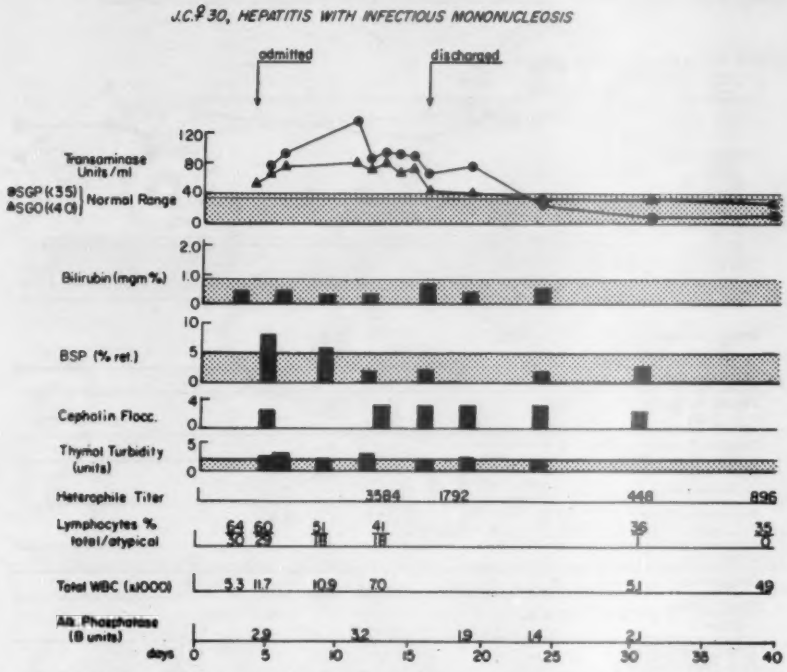


FIG. 4. Depicts the SGP-T and SGO-T alterations over a 40 day period in a patient with acute hepatitis secondary to infectious mononucleosis.

days following the onset of symptoms and was discharged improved on the forty-second hospital day. The remaining 10 patients with infectious hepatitis and two additional patients with homologous serum hepatitis had peak SGP-T levels from 2,200 to 120; in each case the peak and serial values of SGO-T activity were less than the corresponding SGP-T activity.

Of eight patients with infectious mononucleosis, three had associated hepatitis and showed significant SGP-T and SGO-T alterations, but of less magnitude than in viral infectious or homologous serum hepatitis. One of the three, J. C. (figure 4), was admitted for study and treatment of cervical

adenopathy and generalized malaise. Both her SGP-T and SGO-T were elevated early in the course of the infectious mononucleosis hepatitis when the Bromsulphalein retention and cephalin flocculation were abnormal. The remaining five patients with no evidence of hepatitis had persistently normal SGP-T and SGO-T activity.

L. F. (figure 5) had acute hepatitis one year before coming under our observation. The finding of persistent and comparable increased SGO-T and SGP-T activity suggested the presence of chronic or recurrent hepatitis. Liver biopsy showed chronic hepatitis with postnecrotic cirrhosis.

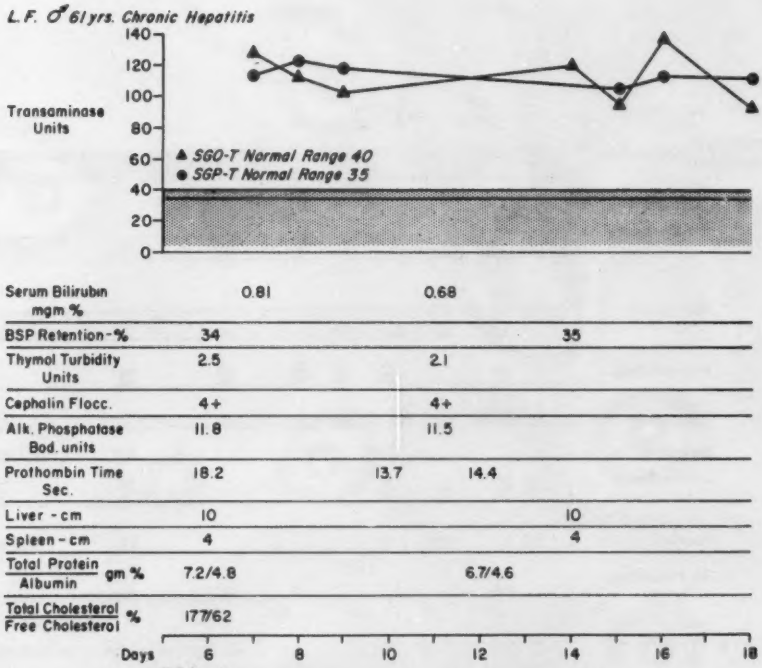


FIG. 5. Shows the SGP-T, SGO-T, liver and spleen size changes, together with usual tests of liver function, in a patient with "chronic hepatitis." Note lack of quantitative relationship between the transaminase and the other data listed.

CIRRHOSIS

Eight patients with cirrhosis of the liver (three proved by biopsy) were studied. In three the SGP-T activity was normal, and in the remainder it varied from 120 to 40 units. In all eight patients the SGO-T was abnormal, ranging in values from 52 to 146 units. All the patients had two or more abnormal tests of liver functions and were adjudged clinically to have cir-

rhosis in relapse. In every instance the SGO-T activity was greater than that of the SGP-T. Figure 6 shows the changes in SGO-T, SGP-T, and other laboratory evidence of liver disease over a 25 day period in a 51 year old male with postnecrotic cirrhosis; he had jaundice, hepatosplenomegaly, ascites and peripheral edema. In five additional patients with clinically inactive cirrhosis, the SGP-T and SGO-T were both within the normal range.

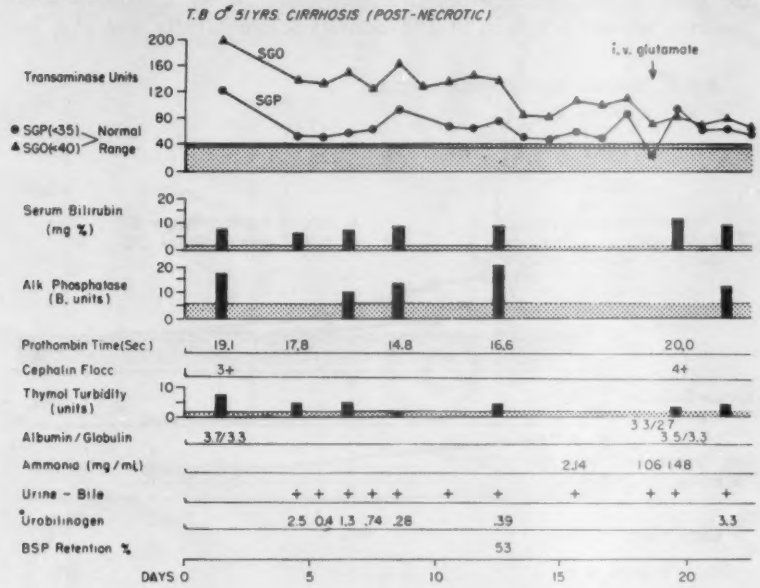


FIG. 6. Describes the alterations in SGP-T, SGO-T and other pertinent laboratory data over a 25 day period in a patient with postnecrotic cirrhosis.

OBSTRUCTIVE JAUNDICE

Six patients with obstructive jaundice were studied. One had cancer of the head of the pancreas with jaundice of three weeks' duration. The SGP-T activity was 300 units preoperatively and fell to normal in 12 days. Three patients had common duct stone with jaundice of two, six and 12 days' duration. The SGP-T activity was 279, 242 and 164 units, respectively, and fell within two weeks postoperatively to within normal range. Figure 7 compares the significant laboratory findings in patient A.G. with common duct stone obstruction. Another patient had incomplete extrahepatic biliary obstruction from enlarged lymph nodes due to lymphoma; the peak SGP-T was 360 units, with a corresponding SGO-T of 136. At laparotomy the obstruction could not be completely relieved, and postoperatively the SGP-T remained at levels of 96 to 104, with corresponding

SGO-T activity of 80 to 91 units. In all the cases of acute and subacute extrahepatic biliary obstruction SGP-T was greater than SGO-T activity.

Metastatic Cancer of the Liver

Of 15 patients with primary and metastatic involvement of the liver with carcinoma and lymphoma, SGP-T was increased in only five. Twelve of the patients had abnormal SGO-T activities. When metastatic disease of the liver effected a rise in SGP-T activity it consistently was of a lesser

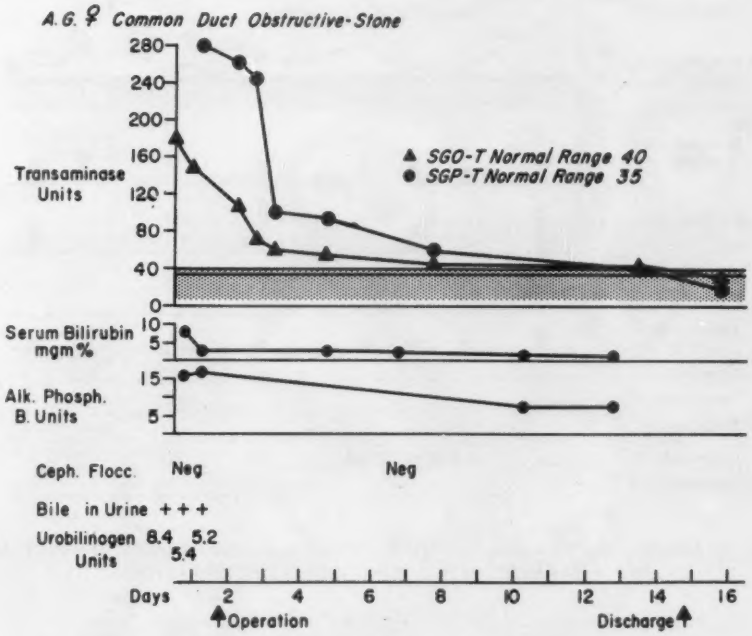


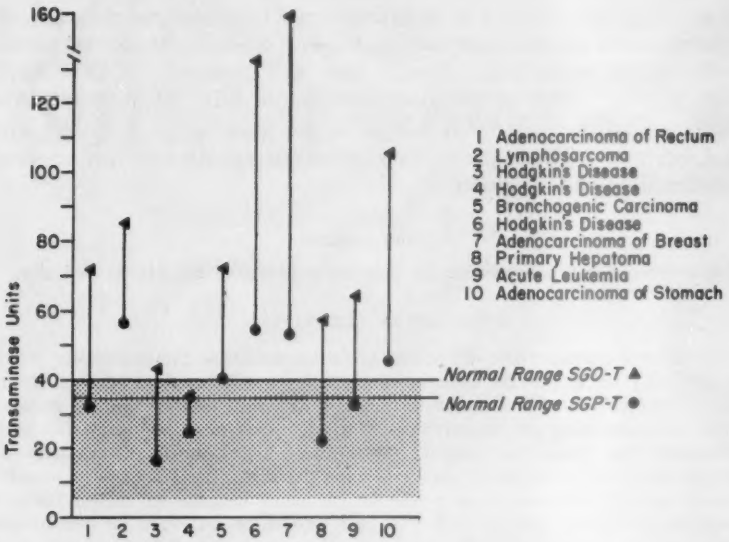
Fig. 7. Compares the changes in SGP-T, SGO-T and other significant laboratory data over a 15 day period in a patient with a common duct obstruction due to cholelithiasis.

increment than the corresponding SGO-T activity (figure 8). It appeared that when metastatic liver disease causes a rise of about 75 units or more in SGO-T activity, a rise in SGP-T is also seen, but that the latter increase is smaller than that of SGO-T activity.

Discussion

The clinical data reported here are too meager to permit any definite conclusion relative to the correlation, if any, between the height of SGP-T elevation and the amount of liver cell damage. It appears, however, that

acute liver cell injury as seen in acute hepatitis results in impressive increments in SGP-T activity. In each case of acute hepatic disease the SGP-T activity exceeded the corresponding SGO-T activity. Although both serum enzymes are altered in the same direction, the serial alterations seen do not necessarily correlate with measurements of liver function. In cirrhosis and metastatic disease of the liver the increment in SGP-T is usually less in magnitude than that of SGO-T. It appears that SGO-T activity is a more sensitive reflection of chronic hepatic disease, and that SGP-T is more readily elevated by acute hepatitis.



COMPARISON OF SGP-T AND SGO-T IN PATIENTS WITH LIVER INVOLVEMENT BY CARCINOMA, LYMPHOMA AND LEUKEMIA.

FIG. 8.

It has been suggested that the increase in SGO-T activity in acute hepatic disease results from the release of liver-cell glutamic oxaloacetic transaminase into the blood stream from damaged liver cells.[6] The presence in hepatic tissue homogenates of considerably less glutamic pyruvic transaminase activity than glutamic oxaloacetic transaminase suggests that the relatively greater increment of SGP-T activity in acute liver disease could not be due solely to release of enzyme from necrotic hepatic tissue. Variations in the release, destruction or excretion of the two enzymes or an unknown metabolic aberration are probably important contributory mechanisms yet to be clarified. The increase in SGO-T following acute myocardial infarction

would appear to be due primarily to release of enzyme from necrotic cardiac muscle. The failure of appreciable elevation of SGP-T to appear following myocardial infarction is probably due to the relatively small amount of GP-T escaping from damaged heart cells. When the released GP-T is diluted in the extracellular compartment it fails to increase the SGP-T activity appreciably.

Summary

The measurement of SGP-T alterations has been found to be a useful tool in the diagnosis and study of acute hepatic disease and appears to be more sensitive than SGO-T in reflecting acute hepatocellular damage. By the simultaneous measurement of SGO-T and SGP-T, it may be possible to differentiate acute from chronic liver cell damage. SGP-T, unlike SGO-T, has the added advantage of usually not being appreciably altered by acute myocardial infarction except in the presence of extensive myocardial necrosis. These preliminary observations require further study for confirmation and definition.

Acknowledgment

The authors wish to acknowledge the technical assistance of Mr. Martin Podgainy.

Summario in Interlingua

Alterationes characteristic del activitate de transaminase glutamic-oxalacetic del sero (SGO-T) se ha provate utile in evalutar le presentia e le grado de lesiones cardio- e hepatocellular. Esseva constatate que le activitate de transaminase glutamic-pyruvic, in comparation con le activitate de transaminase glutamic-oxalacetic, esseva relativemente plus grande in le hepate que in altere histos human. Iste observation suggereva que le transaminase glutamic-pyruvic del sero (SGP-T) esseva possibilemente—a causa de su concentration selective in histos hepatic—un melior indice de lesiones hepato-cellular que SGO-T. In plus, proque le activitate de transaminase glutamic-pyruvic in histos cardiac es basse, necrose myocardial es possibilemente associabile con minor o minuscule alterationes del activitate de SGP-T que alora devenirea un plus specific indice de lesiones hepatocellular.

Transaminase glutamic-pyruvic esseva mesurate a 23 C in seros de 260 normal humanos, e le activitates habeva un valor medie de 16 ± 9 unitates per ml per minuta. Le activitate de SGP-T e de SGO-T esseva studiate in patientes con varie statos pathologic, incluse acute hepatitis infectiose, hepatitis a sero homologe, cirrhosis, extrahepatic jalnessa obstructive, carcinoma primari e metastatic del hepate, e acute infarcimento myocardial.

Esseva constatate que mesurationes de alterationes de SGP-T es un factor de utilitate in le diagnose e le studio de acute morbo hepatic. Il pare que SGP-T es plus sensibile que SGO-T como indicator de acute lesiones hepatocellular. Per medio del mesuration simultanee de SGO-T e SGP-T, il pare possibile differentiar inter acute e chronic morbo hepatic. SGP-T ha in plus le avantage—non trovate in SGO-T—que illo remane usualmente sin significative alteration in consequentia de infarcimento myocardial, excepte in casos de extense necrosis cardiac. Iste observationes es preliminari e require studios additional pro lor confirmation e extension.

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TREATMENT OF MULTIPLE SCLEROSIS WITH LOW-FAT DIET: RESULT OF SEVEN YEARS' EXPERIENCE *

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Experimental therapy of chronic diseases demands patience and persistence if a definite conclusion is to be reached. The period of therapy must bear some relationship to the normally expected duration of the disease. Multiple sclerosis is thought to have an average duration of 20 to 25 years. The same person or persons should evaluate the patients periodically from the beginning to the end of the study. It hardly need be added that the same patients must be followed continuously during the entire period of treatment.

It is not necessary, but would probably be helpful, that the progress of the study be reported from time to time. This would give the investigator an opportunity seriously to evaluate his data at regular intervals and to crystallize his own thinking on the subject. It would also allow his critics an opportunity to review the study and to point out inconsistencies in the data. The present study of the effect of low-fat diet on multiple sclerosis was reported first at the end of three and one-half years of observation,[1] and again at the end of five and one-half years.[2] At present the study has been in progress nearly seven and one-half years.

Historical Background

It has been known for some years that the prevalence of multiple sclerosis varies in different parts of the world. In 1918 to 1922 a survey in Switzerland revealed that the prevalence of the disease was high in the northern, German-speaking part of the country, and very low in the southern, Italian-speaking part. In the southwestern part of Switzerland, where French culture predominates, the prevalence of multiple sclerosis was intermediate.[3] A survey in Denmark in 1934 indicated that the prevalence of multiple sclerosis was nearly twice as great in rural as in urban areas.[4] More recent mortality statistics [5] have indicated that multiple sclerosis occurs with relatively high frequency in northern Europe, Scandinavia, England, Canada and the northern part of the United States. A low frequency of

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occurrence was found in Italy, in southern France, and in the southern part of the United States. These studies relative to North America were confirmed by subsequent studies of prevalence of the disease.[6] Another study has shown that the prevalence of multiple sclerosis is low in South Africa.[7] It is generally felt that in the Caribbean and Mediterranean areas and in the Near East, India, China and Japan the prevalence of the disease is also low. Many of these latter views are based on clinical observations not controlled by statistical studies. Reference to the United Nations Food and Agriculture Organization[8] shows that the fat intake is above 100 gm. daily in the countries which have just been considered to have a high prevalence of multiple sclerosis. The fat intake is below 50 gm. daily in those countries where the prevalence of multiple sclerosis is considered low.[9]

During World War II the fat intake in urban areas decreased about 50% in occupied Norway, Denmark and Holland. Following the war the fat intake in Norway returned to normal in approximately two years. In Denmark and Holland the fat intake continued low for at least three years. Observations of the hospital admissions of multiple sclerosis suggested a possible direct relationship between fat intake and number of admissions of patients with multiple sclerosis. Observations of displaced peoples and of prisoners-of-war indicated a similar possible direct relationship of fat intake to the frequency of multiple sclerosis.[9] A post-war survey in Norway showed that the incidence of multiple sclerosis from 1935 to 1948 was low along the coast and relatively high in the inland farming areas. It was particularly high in farming areas isolated by virtue of great distances, fjords or mountains. Food surveys in different areas of Norway indicated that the fat intake, particularly the butter fat intake, was high where multiple sclerosis had a high incidence, and low where multiple sclerosis had a low incidence.[10]

Because of the possible relationship of fat intake to the incidence of multiple sclerosis, our studies of the effect of low fat diet on multiple sclerosis were undertaken.

Material and Methods

During the period from December, 1948, to July, 1954 (approximately five and one-half years), studies were initiated in 264 patients with multiple sclerosis at the Montreal Neurological Institute. All but a few of these patients with multiple sclerosis were seen more than once; many of them were admitted to the Montreal Neurological Institute for diagnosis, and most of the remaining were seen by other neurologists. We have managed to maintain continuous contact with 210 of the 264 patients, and 153 of these have remained on the low-fat diet.

The low fat diet has remained unchanged except for minor alterations in the prescribed amounts of the fat intake. During the first year the diet contained 20 to 30 gm. of fat, mostly milk and animal fats. In the sub-

sequent two years the saturated animal and milk fats were limited to 20 gm. daily. To this were added 5 gm. of cod liver oil and 10 to 15 gm. of vegetable oil or fish oil daily. At the end of approximately three years, milk fat was eliminated from the diet completely, and the prescribed total fat intake was reduced to 30 gm. daily. Since then the diet has contained 15 gm. of animal or hard fat (including hydrogenated vegetable oil, such as shortening and margarine) and 15 gm. of vegetable or fish oil. The protein intake has been maintained at 50 to 60 gm. or more daily, depending upon the weight and dietary habits of the patients, and the balance of the caloric need has been obtained from carbohydrates. The caloric intake has been the same throughout the entire study. Our records would indicate that the average caloric intake of a 130-pound woman was 1,700 calories, and for a 145-pound man, 1,900 calories. These estimates may be low, since the patients were concerned primarily with recording the fat intake and may have forgot to record other foods at times. As a rule, the patients have remained 5% to 10% under what might be considered normal average weight. One multiple vitamin capsule, containing vitamins A, B complex, C and D, is taken daily, and whole wheat bread is recommended. Skimmed milk is used by all patients as a source of protein. Most patients eat at least one egg daily.

The dietary intake of the patients is checked every two weeks at first, and later at monthly intervals. The patient records all the food he eats for each meal in a notebook provided for this purpose. From this the dietitian determines the food intake and makes necessary adjustments. The patient's weight is checked at each visit, and rapid changes in weight are carefully watched for. The diet is mimeographed (see Appendix), and special recipes substituting vegetable oils for animal and butter fats have been assembled and are furnished to the patient.

Various supportive measures, such as physical therapy, use of drugs to relieve nervous tension, and other medical treatments, have been employed as indicated. In this group of patients none of the ambulant and only a few of the nonambulant patients have received physical therapy regularly.

Since our move to Portland, Oregon, we have been in contact with the patients every six weeks to three months, and have seen them once a year, in the month of June. The patients keep careful records of their diet, weight and physical condition in small notebooks, and these records are sent to us periodically. It should not be overlooked that prior to our move to Portland the patients had been in our care for from one and one-half to five and one-half years, and were well indoctrinated with our methods.

Control Material: During the first years of our study we did not have a large enough group of patients with multiple sclerosis who consumed a normal diet to serve as a control for those who received the low fat diet. We therefore used the three year period preceding the low fat diet as a control for each of these patients. These data, with other pertinent facts concerning

the first 47 patients to come under our control, and the classification of each patient, are included in the single table and in charts 1 and 2 of the preliminary reports.[1, 2] There has been no change during the seven and one-half year period in the control of this material. The 47 patients reported in the preceding papers are included in this report. To these have been added 107 other patients who have been on the low fat diet a somewhat shorter time. All 153 patients have been interviewed at regular intervals by the same observers during the entire one and one-half to seven and one-half year period of observation. As far as possible, their progress, including exacerbations and remissions, has been evaluated and recorded uniformly during this period.

Results

Before we discuss the results of our treatment it is necessary to consider some aspects of the course of the disease, since the stage of the disease in which treatment is started has determined the efficiency of the therapy. Typically, the disease is characterized by "attacks" composed of an exacerbation followed by a remission (figure 1). The exacerbations may be abrupt or slow in onset, and in a few hours to a few days the maximal disability develops. After a period of stabilization a remission usually occurs and the disability may disappear almost entirely. The frequency of the "attacks" varies greatly in different individuals. An average of approximately one attack per 10 to 12 months per patient has been reported in a large multiple sclerosis population in Denmark,[11] and also in the multiple sclerosis population now under consideration.[1]

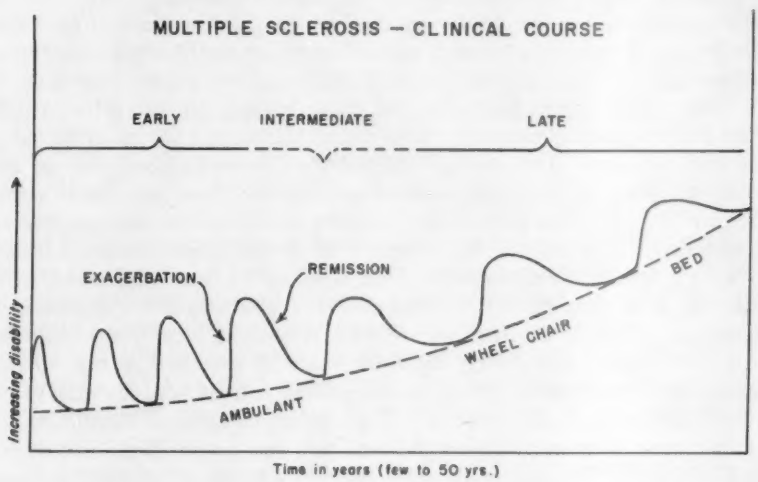


Fig. 1. Exacerbations and remissions at different stages of multiple sclerosis.

Early in the disease the remissions may be quite complete, and between attacks the condition of the patients either continues to improve or remains unchanged. As the disease progresses the remissions are less complete, and between "attacks" the condition of the patients gradually deteriorates. This important point differentiates our *early* from our *late* group of patients. Because of the slow progress of the disease it is often difficult to categorize patients when they are first seen. These uncertain cases are now referred to as *intermediate cases.*

Two clinical features of the disease are available as indicators of progress of the disease. First, one can compare the frequency and severity of attacks before and after treatment; second, one can observe the performance of patients prior to and while on treatment. Either or both of these criteria can be used successfully if correctly evaluated, and recorded over a long enough period, in a large enough group of patients. *The speed or degree of recovery from a single or even from several attacks of disease—namely, remissions—is not a reliable index of therapeutic success.*

A. *The frequency and severity of exacerbations* were studied in the first 47 cases which came under our observation.[1, 2] Careful histories were obtained. The patients were questioned on at least two occasions. They were then instructed to write down their own histories with the help of friends or family. Finally, hospital and out-patient records were examined. From these accumulated data the "attacks" during the three year period prior to treatment were recorded. During treatment the patients were seen at regular intervals and the "attacks" were recorded. Because of our closer contact with the patients, records of "attacks" were probably more complete during the period of treatment than before treatment.

The effects of the low fat diet on the frequency and severity of exacerbations in the 34 patients with early and intermediate multiple sclerosis * were analyzed first. These patients were all ambulant and many were working full time. They were chosen because exacerbations are more frequent in active than in inactive patients. Also, the exacerbations are easier to recognize and evaluate. The average frequency of exacerbations prior to and during six years of treatment on the low fat diet in these patients is shown in figure 2. The solid black points on the figure show the average interval between attacks when attacks occurring after significant dietary indiscretions are eliminated from consideration. During the three year period prior to the use of the low fat diet the interval between attacks was approximately 11 months. During the first year it was 34 months, during the next two years, 60 months, and during the sixth year, 96 months. When no corrections for dietary indiscretions are made, the periods between attacks are as indicated in figure 2 by circles. These intervals were 18 months during the first year, 45 months during the next two years, and 76 months during the sixth year. The solid point surrounded by a circle at five years indicates

* In our earlier reports these two groups were included together as early cases.

a slightly higher incidence of attacks than expected. This was during the year preceding our move to Portland, and may indicate the influence of anxiety upon the disease.

Equally significant was the fact that the exacerbations which occurred in patients on the low fat diet became progressively less severe. This is indicated in figure 2 by the width of the shaded area. At the end of three years the few exacerbations that did occur were mild, and were often referred to by the patients as "fluctuations." Periods of deep fatigue lasting a few days to weeks developed from time to time. They were not accom-

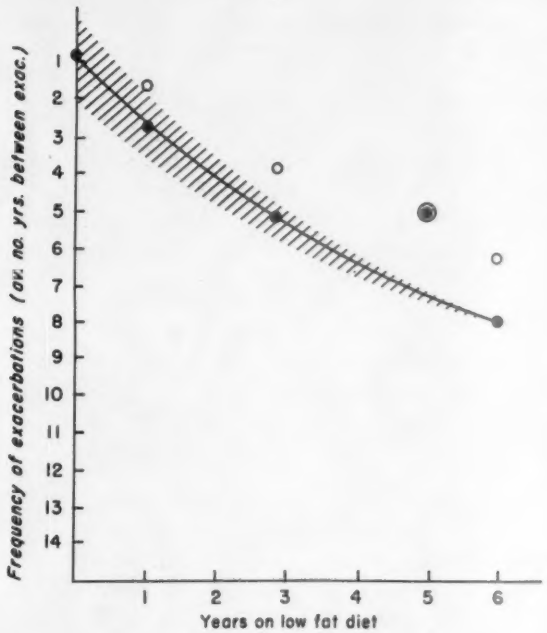


FIG. 2. Explanation in text.

panied by clear-cut neurologic deficits, and vanished much as they appeared, leaving no residua. These "attacks" of fatigue alone were not considered as exacerbations of multiple sclerosis. It is recognized, however, that they probably indicated activity of the disease.

The first 13 late cases were also observed closely in a similar way during the first six years on the low fat diet. The frequency and severity of exacerbations were even more markedly reduced than in the 34 early and intermediate cases.

B. *Evaluation of performance.* Our first 47 patients have been on the low fat diet an average of six years as of June, 1955, when the patients were

last interviewed. Our studies indicate that, in general, the performance of the early and intermediate cases improved or remained unchanged during this period, whereas the performance of the late cases deteriorated. Only three of the 34 early and intermediate cases deteriorated during the first three years on the diet. Nine patients were able to work full time when placed on the diet. At the end of three years 24 were working full time, and all were ambulant. At the end of five years 23 were working full time and one patient was no longer known to us. Although three more cases had shown some deterioration at the end of five years, this was so slight that the performance category of these patients was unchanged. All patients in this group were still ambulant. At the end of six years (June, 1955), two patients previously barely ambulant had become confined to a chair, and one patient able to work part time was now ambulant and not working. The same 23 patients were still working full time. Ten of the 13 late cases had deteriorated steadily. One patient was still able to work part time, and six others were ambulant. For further analysis of our first 47 patients to be placed on the low fat diet the reader is referred to earlier papers.[1, 2]

For further analysis, the 47 patients just described were included with 107 patients on diet for shorter periods of time. One hundred twenty-seven of these were interviewed and examined in June, 1955, and the other 26 patients have been in close enough contact with us so that we know with confidence their performance as of that date. The duration of therapy on the low fat diet varied from 1.5 to 6.5 years as of June, 1955. The average duration of therapy for the entire group of 153 patients was 45.6 months. For the purpose of evaluation of therapy, the patients have been classified as early, intermediate or late, depending upon their condition when placed on diet (table 1).

There were 59 early cases. All but five of these either improved or remained unchanged. Of the five cases that deteriorated, two followed the diet poorly and probably should have been eliminated from the analysis. The other three cases showed slight but definite deterioration, although in each instance they continued working full time at their jobs. It should be emphasized that all of the early cases were working either full or part time, and were fully ambulant.

Twenty-four of the 36 intermediate cases have remained the same or improved; 12 have deteriorated. Twenty of the 58 late cases have remained the same or improved, and 38 have deteriorated.

Three patients on the low fat diet have died, one from cancer of the bowel, a second from myocardial infarction; the cause of death in the third is not known. These three patients are not included in our group of 153 cases now under consideration.

The data in the table relative to the patient-age when the low fat diet was started, and the duration of multiple sclerosis when the low fat diet was started, indicate that the age of onset of multiple sclerosis in early, inter-

TABLE 1

	Early		Intermediate		Late		Totals	
Duration M.S. before L.F.D. (years)	2.6		5.8		11.2		6.6	
Age when L.F.D. started	30.6		33.3		39.2		34.5	
Duration L.F.D. (months)	43.3		49.1		45.7		45.6	
	No.	%	No.	%	No.	%	No.	%
No. M.S. cases	59		36		58		153	
Improved	44	92	14	67	6	35	64	64
Unchanged	10		10		14		34	
Deteriorated	5	8	12	33	38	65	55	36
Diet control:								
Good	40	87	13	70	32	81	85	80
Fair	11		12		15		38	
Poor	8	13	11	30	11	19	30	20

M.S., Multiple sclerosis; L.F.D., low fat diet.

mediate and late cases was approximately the same, 27.5 to 28 years. These are the only statistical data available in this study to indicate a uniformity of the average patient population in each clinical subgroup.

Many of the patients who improved while on the low fat diet were placed on the diet during activity of the disease. Temporary improvement would have been expected in most of these had no therapy been given. However, the maintenance of an improved state or even unchanged state for so long a time is probably significant.

Dietary control was good to fair in about 80% of our patients during the entire period of observation (table 1). Poor control was indicated when patients discontinued the diet periodically, or doubled the intended hard fat intake for a week or longer. Good dietary control indicated that the patients were almost always within 5 gm., more or less, of their hard fat and oil intakes. It has been noted that patients who have followed the diet closely have had the fewest exacerbations, and in general have done well. There were notable exceptions to this: three of the early patients who deteriorated had followed the diet very faithfully.

These data support our tentative conclusion that patients that we are able to classify as early when placed on the diet do very well for a period averaging nearly four years. The intermediate cases do a little less well, and the late cases tend to continue to deteriorate steadily, even though "attacks" are much less frequent or even absent.

By relating the years of disease before the start of treatment to the effects of treatment on all patients in this group, one obtains interesting supportive data for this tentative conclusion. On the average, patients having multiple sclerosis five years or less prior to therapy do well on the low fat diet. Those having multiple sclerosis seven years or more prior to treatment continue to deteriorate on this same therapy (figure 3).

Discussion

It is becoming increasingly evident that the low fat diet alters the course of multiple sclerosis. Over a period of six years a substantial decrease in both frequency and severity of exacerbations has resulted. Prior to use of

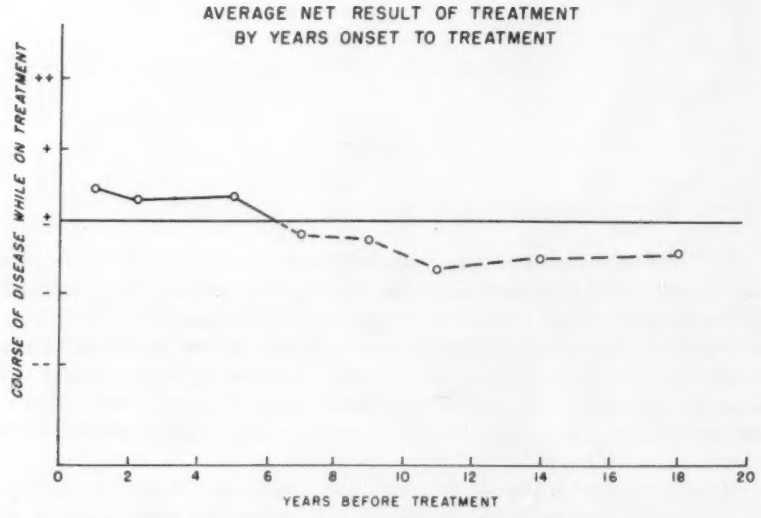


Fig. 3. Positive (+) and negative (−) results from treatment in relation to duration of disease prior to beginning of treatment.

the low fat diet, patients were averaging about one exacerbation every year. During the sixth year on the diet these same patients were averaging one attack every eight years. During most of this six-year period these patients generally improved, and 23 of this group of 34 early and intermediate cases worked full time. Prior to use of the low fat diet, only nine of these patients were working full time.

Analysis of all 153 patients indicates an over-all improved or unchanged state in 64% during an average observation period of nearly four years. Considered alone, this is an impressive figure. It becomes even more impressive when one considers the early cases alone. In this group, 92%

have not deteriorated. Two of the five cases that deteriorated did not follow their diet, and the other three are still able to work full time. It is becoming clear that any benefit from the low fat diet was derived particularly by those in whom the disease was in its early phase. In the late cases, continuing deterioration has been the rule, although this deterioration has been very slow. It appears that if the course of the disease is to be significantly altered, treatment must be started early.

The effect of diet seems to be cumulative. The longer patients are on the diet, the better they seem to do. This impression is supported by the gradual decrease in the frequency and severity of exacerbations observed over the six-year period. Also, the general well being of the early patients, and their energy, seem to increase progressively as the period on diet lengthens.

It is clear that the disease has not been cured by the low fat diet even in the early cases, since clear-cut exacerbations were noted in a few patients who followed the diet carefully. However, reduction in the severity and frequency of the exacerbations was substantial, and, despite the recurrence of minor exacerbations, most patients improved generally and became capable of increased work during the period that they consumed the low fat diet. It seems likely that a high fat intake is an important factor in causing a high morbidity of the disease. Another study [12] has shown that variations in the outside temperature may be another contributing factor, but this is of far less importance than the fat intake.

It is impossible at present to *conclude* that the diet has permanently improved or will permanently maintain the performance of patients with multiple sclerosis. Many investigators have commented that patients with multiple sclerosis are very suggestible, and that approximately 40% of a sizable multiple sclerosis population will respond favorably to almost any procedure offered as therapy. Most reported trials of therapy have been relatively short, usually six to 18 months. One of the longer reported studies was of the effect of Dicumarol by Putnam,[13] and this study averaged 18 months per patient. About 40% of our 153 patients improved, and can probably be considered to have been in remission. Since the average length of remission (period between exacerbations) was about one year prior to use of the low fat diet, any treatment started at the beginning of remission would have been expected to benefit 40% of our patients for approximately one year. On the low fat diet the improvement has lasted nearly four years, and an additional 24% of our patients have failed to deteriorate. The present investigator feels that it is unlikely that the low fat diet has been without beneficial effect, since, first, only 36% of the patients have deteriorated; and second, the deterioration has been very slow; and third, the benefit or maintenance of health has lasted nearly four years.

It can be argued that our reported results are precisely what one would expect from the natural course of the disease: early in the disease patients

remain relatively well, and later they deteriorate. We are unable to disprove this argument, since we do not have a group of patients that we feel can adequately function as controls, nor is such a group of patients available in the literature. It is hoped that continued follow-up of our patients will resolve this conflict definitely. We plan to continue this study for a minimum of four more years.

If we assume that the low fat diet stops or significantly reduces activity of the disease, then we need to explain why so many late cases of multiple sclerosis continue to deteriorate. Two possible explanations come to mind: First, vascular changes such as Macchi has described may lead to progressive tissue ischemia and degeneration of nervous tissues.[14] Second, the dense glial scars which are found in the brain and spinal cord may slowly contract about and destroy neurones.

In two previous communications the pathogenesis of the nervous lesions in multiple sclerosis was discussed.[1, 2] It suffices here to point out that, in the opinion of the present writer, the vascular system, and in particular the blood, may be involved.

Conclusion

Six and one-half years' experience with a low fat diet in the treatment of multiple sclerosis is summarized. The diet appears to reduce the frequency and severity of exacerbations of the disease. In doing this, the over-all severity of the disease appears to be lessened, and the performance of 64% of a total of 153 patients has been improved or held stable for nearly four years. Early cases of the disease appear to benefit most. Only 8% of 59 early cases deteriorated during a period averaging 43.3 months. About 65% of 58 late cases, and 33% of 36 intermediate cases, deteriorated in this same period.

The total period of observation has now been sufficiently long to give us some confidence in our observations. We must not, however, overlook the fact that we are dealing with a disease having an average duration of 20 to 25 years. Our conclusions must still remain tentative.

Appendix

Low-fat, high-carbohydrate, moderate-protein diet.

Your diet will contain 3 tsp. (15 gm.) of hard fats (animal fats, margarine, lard, and shortening) and 3 tsp. (15 gm.) of vegetable oil or a substitute a day. As far as possible, the intake of fat should be evenly distributed throughout the day. All patients should consume at least one egg and 1 tsp. (5 c.c.) of cod liver oil daily. Fats or oils used for cooking or baking must be included when determining the daily fat intake.

Foods forbidden on your diet.

Whole milk, butter, cream, cocoa and chocolate, and all foods containing these substances, such as pastries, pies, steamed puddings, cake puddings, cakes, cookies, doughnuts, chocolates, chocolate bars, cocoa, hot chocolate, chocolate-flavored drinks, cheese, ice cream, and cream sauce made with butter and/or whole milk, and canned spaghetti with meat or meat sauce.

Foods permitted in any quantity.

Boiled codfish, halibut or haddock, scallops, lobster, crab—any fish which contains no oil
All vegetables
All clear soups
White or brown bread
All cereal products
Skimmed milk, at least three glasses a day, or buttermilk
Cottage cheese
All fruits
Desserts made from egg whites
Cream soup made with skimmed milk
Maple and corn syrup
Water ice
Rice, tapioca, or cornstarch puddings made with skimmed milk, no egg yolk
Jello
Fruit juices
Vegetable juices
Clear tea or coffee
Carbonated beverages
Jam and jelly
Molasses
Marmalade and honey
Sugar
Sphaghetti and macaroni
Fresh or tinned clams and oysters
Seasonings

Foods permitted in limited quantity.

Soda crackers
Graham wafers
"Social Teas"
Arrow biscuits or tea biscuits

Substitutes of 1 tsp. of hard fat.

2 oz. (60 gm.) chicken, beef, roast leg of lamb, ham, veal, beef sausage, liver, and turkey
1 egg
3 slices bacon, fried crisp and drained well
1 slice of bologna, salami or liverwurst (1 oz.)
½ lamb chop (1 oz.)
1 frankfurter
1 pork sausage
1 slice of roast pork (1 oz.)
1 oz. goose or duck
1 tsp. margarine, lard or shortening
½ pork chop (1 oz.)

Substitutes for 1 tsp. of vegetable oil.

1 tsp. of olive oil, corn oil, cottonseed oil, wheat germ oil, Mazola and Wesson oil, cod liver oil
5 olives
2 tsp. of salad dressing or mayonnaise
15 peanuts
4 small anchovies
2 tsp. pure peanut butter (not hydrogenated)
2 oz. tuna fish or trout
2 oz. of canned or fresh salmon
1 oz. of mackerel
1 oz. of herring, sardines, or kippers

Summario in Interlingua

Es reportate observationes basate super septe annos e medie de experientia con le uso de dietas a basse contento de grassia in le tractamento de sclerosis multiple. In iste dietas le ingestion de grassia es restringite a 30 g per die. Dece-cinque grammas es grassia solide o animal, le resto es grassia vegetal o oleo de pisce. Le ingestion de proteina amonta a circa 60 g per die. Le remanente requirimentos caloric es satisfacite per hydratos de carbon. Sub iste conditiones le majoritate del patientes mantene un peso de circa 5% infra le norma communmente stipulate pro lor altor.

Patientes qui ha observate iste typo de dieta strictemente ha experientiate reducite frequentias de attaccos a transverso varie periodos, con un duration medie de sex annos. Ante le adoption del therapia a dietas de basse contentos de grassia, un gruppo de 33 casos precoce e intermediari manifestava un frequentia medie de exacerbationes de un in 11 menses. Al fin de sex annos de dieta a basse contento de grassia, le mesme patientes habeva un frequentia medie de attaccos de un in 96 menses. Concomitantemente le severitate del attaccos esseva reducite.

Un total de 153 patientes con sclerosis multiple esseva observate sub le conditiones de un dieta a basse contento de grassia durante un periodo medie de circa quatro annos ante le mense junio 1955. Lor casos esseva dividite in le tres gruppos de precoce, intermediari, e tardive, secundo lor condition al tempore quando illes adoptava le dieta a grassia reducite. Omne le 59 casos precoce, con solmente cinque exceptiones, ha remanite static o se ha meliorate. Duo del cinque exceptiones concerne patientes qui observava lor dieta inadequatemente. Inter le 36 casos intermediari, 24 ha remanite static o se ha meliorate e 12 ha manifestate un deterioration. Vinti del 58 casos tardive ha remanite static o se ha meliorate, durante que 38 ha manifestate un deterioration. Quando le gruppo total de patientes es considerate, 64% ha remanite static o se ha meliorate in le curso de un periodo medie de quatro annos e le altere 36% ha manifestate un lente sed definite deterioration. Pro esser efficace, le tractamento a dieta de basse contento de grassia debe esser initiate ante que grados significative de invaliditate se ha disveloppate.

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THE FRACTIONATION OF IMPORTANT CONSTITUENTS OF GASTRIC JUICE OTHER THAN HYDROCHLORIC ACID * †

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The present communication is a very preliminary report, essentially a statement of progress on an attempt to sort out the biologically important ingredients of the gastric juice.

The importance of the stomach in the bodily economy was recognized in the early eighteenth century when the wealthy and indefatigable French scientist de Réaumur made his birds swallow tiny perforated metal containers in which he had placed particles of food.[1] Later he pulled up the containers and found that the food had been dissolved out of them. A few years later the brilliant Italian investigator, Abbé Spallanzani, first demonstrated that the solvent power of the stomach resided in the fluid which it contained.[2] He obtained gastric juice from himself by swallowing a dry sponge attached to a string, retrieving it and then squeezing it out. Thereby he showed that gastric juice removed from the body was capable of digesting meat.

In the early nineteenth century William Prout,[3] practicing in London, demonstrated for the first time that the gastric juice contained hydrochloric acid. The mechanism of digestion by the gastric juice had still not been discovered, however, and was not discovered until Beaumont,[4] working with his famous fistulous patient, Alex St. Martin, showed that digestion of meat is accomplished because the hydrochloric acid is supplemented by another substance present in the gastric juice. Thus the existence of the enzyme pepsin was first recognized. Pepsin was separated from the gastric juice and given its name in 1836 by Theodor Schwann.[5] More than a century later it was finally purified and crystallized by Northrop.[6] In the intervening years other digestive enzymes had been discovered in the gastric juice, and Castle [7] had made his signal contribution, the identification of the intrinsic factor.

Although more than 25 years have elapsed since Castle's discovery, no disease other than pernicious anemia has been identified with a deficiency

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of gastric secretion. It was partly because it seemed likely that there must be other intrinsic nutritional deficiencies that we undertook the attempt to separate human gastric content into its component fractions.

During the long period when the gastric secretions failed to share with other body fluids the attention of the analytical chemist a great deal was learned about the constituents of the blood, of urine, of ovarian cyst fluid and even of the aqueous and vitreous humors of the eye. Perhaps biochemists hesitated to attempt the fractionation of the complex mixture which is gastric juice because it is so consistently contaminated by salivary and even duodenal secretions and is virtually impossible to obtain in its pure state without an operative procedure.

Our interest in the gastric juice began 15 years ago with a concern with the mechanism whereby mucus was able to protect the delicate lining of the stomach against the corrosive effects of the acid-pepsin mixture. In a study of so-called gastric irritants, it was determined that no substance that could conceivably be classified as food was so potentially irritating as the fluid which the stomach itself secreted and contained normally.[8] The protection was no mere acid-neutralizing effect. The mucous layer was capable of protecting the columnar cells of the gastric mucosa against alkalis as well. Neither was the protective action explainable in terms of physical insulation, because the mucous "barrier" had to allow for secretion and absorption through it. It appeared that an understanding of the protective properties of mucus required the development of a fractionating procedure for gastric content which would separate out the various known large molecular components, such as pepsin, rennin, lysozyme, intrinsic factor and the blood group substances, leaving the remaining substances for individual study.

Adequate study of the large molecular components of the gastric content presupposes their separation in as near their native state as possible. Earlier attempts at separation via technics successfully used on blood serum, such as electrophoresis and cold alcohol precipitation, were disappointing because the separation did not sort out the biologic activities.[9] Peptic activity, for example, appeared in several fractions, as did intrinsic factor activity. In our studies we therefore turned to ultracentrifugation and paper chromatography,[10] and finally, after both of these had also failed to fractionate the gastric content according to biologic properties, we turned to a new technic based on the principle of ion-exchange chromatography. Utilizing this technic, briefly described elsewhere,[11] we have been able to identify and separate into fractions three biologically active components of human gastric content, namely, blood group A substance, pepsin and intrinsic factor. We are of course attempting to purify these substances further, but at the moment the blood group A substance is as potent as any as yet described that has been prepared from other sources such as ovarian cyst fluid. The pepsin has activity of the order of 75% of that displayed by the material purified by Northrop from hog stomach. Intrinsic factor activity was

demonstrated with as little as 2 mg. of material prepared from human gastric juice.[12]

After we arrived at a reasonably standardized procedure for fractionating the gastric content, our study took three somewhat divergent paths: (1) the search for additional biologic activities among the components which separate in the effluent from the column; (2) further purification and ultimate chemical analysis of these components; and (3) comparisons of the chromatographic patterns obtained from normal subjects with those having a variety of bodily diseases and disorders. In the latter category we have been particularly interested in muscular dystrophy, and have accordingly begun to test the gastric juice of individuals with various forms of muscular dystrophy in the resin column. This has been accomplished slowly, because two and one-half weeks are required to make a single fractionation procedure. To date, however, the chromatographic patterns obtained from three subjects with dystrophia myotonica have been so strikingly similar and so characteristically different from the normal that it appeared worth while to report them.

Results

Seven experiments were carried out on the gastric juice of three subjects with typical dystrophia myotonica. The specimens were prepared and tested on the resin column according to the method already described.[11] The analysis of the effluent from each resin column yielded a strikingly similar pattern, which differed from the normal chiefly by the lack of a protein peak at pH 6.1. The other peaks were present, although somewhat smaller than average, and peptic activity in each specimen was approximately normal (40 to 57 P.U.) (Hb. mg. dryweight $+ 10^{-4}$). Figure 1 illustrates the appearance of the chromatogram obtained from the gastric content of these patients with dystrophia myotonica in comparison with the normal.

Discussion

The significance of this apparent abnormality in the gastric content of patients with myotonic dystrophy is not known. The work of other investigators has suggested that the pathogenic mechanism of dystrophy may involve an intrinsic nutritional deficiency.[13] Pappenheimer [14] showed that rabbits fed a diet deficient in vitamin E develop a myopathy histologically similar to dystrophy and accompanied by spontaneous creatinuria. Although the ubiquity of vitamin E in ordinary foods precludes the possibility that a shortage of vitamin E in the diet may play a rôle in muscular dystrophy as it occurs in humans, the possibility exists that utilization of vitamin E in muscle metabolism may require the presence of a principle secreted by the normal stomach, an intrinsic factor. This notion gained support from the studies of Milhorat,[15] who showed that urinary creatine

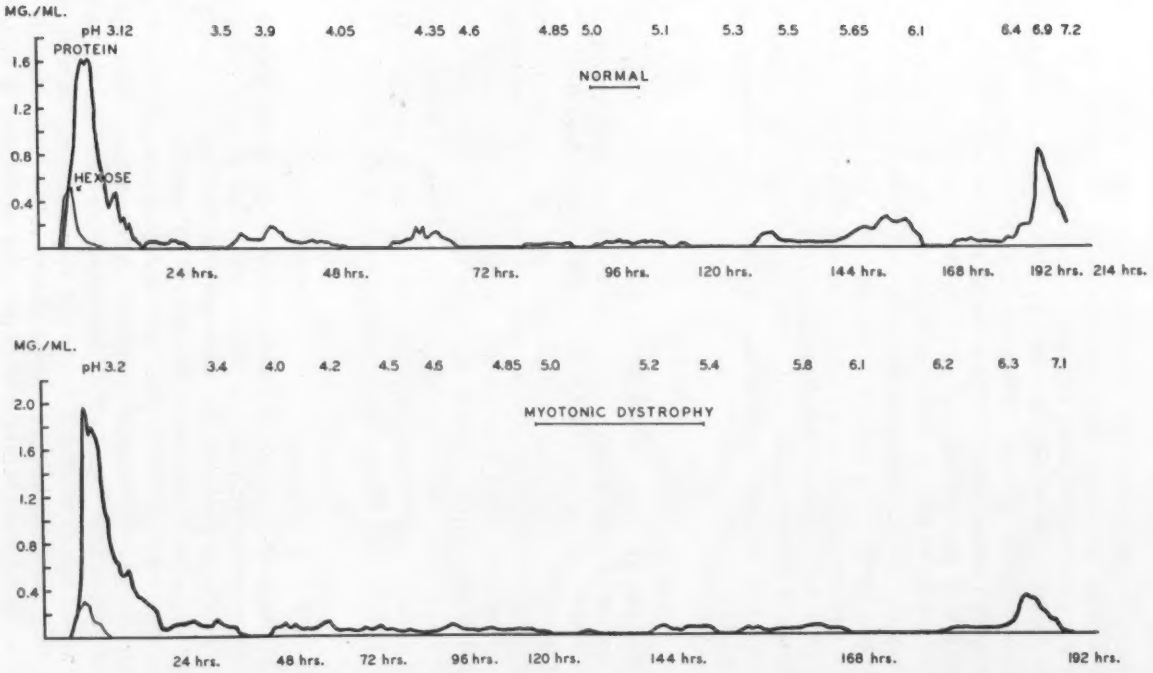


FIG. 1. Pattern obtained by testing the effluent from the resin column by the ninhydrin and anthrone reactions. Major difference between the pattern of gastric content from healthy subjects and from patients with dystrophia myotonia appears to be at pH 6.1.

excretion in patients with progressive muscular dystrophy was sometimes reduced when they were fed vitamin E which had been incubated with gastric juice from healthy individuals.

Although the findings of the present study would appear to support this general concept, the data are too fragmentary to allow of any inference. They have been presented as an illustration of the possible clinical usefulness of a technic which affords a reasonably satisfactory fractional pattern for the large molecular (nondialyzable organic) components of human gastric content. Currently we are making comparisons of patterns of gastric content in a variety of gastric and systemic disorders and diseases.

Conclusion

A clinical application of a recently described method for fractionating large molecular components of human gastric content has been suggested. As a prototype, attention has been called to the absence of a normally occurring protein peak observed consistently in seven tests of the gastric content of three subjects with myotonia dystrophica.

Summario in Interlingua

Omne studio religiose del componentes a grande moleculas in le succo gastric require un processo de fractionation que permitte le separation del mixtura complexe de maniera que omne substantia pote esser studiate individualmente in re su activitates biologic. Previe essayos de effectuar iste separation per medio del technicas applicate con successo a seros de sanguine esseva disappunctante in tanto que le resultatos non constitueva un assortage del activitates biologic. Le autores ha disveloppate un nove methodo pro le fractionation del nondialysabile componentes de succo gastric, basate super le principio del chromatographia a columnas de resina. Iste technica effectua un satis nette separation de tres activitates biologic, i.e. (1) gruppo sanguinee A, (2) pepsina, e (3) factor intrinsec. Le technica etiam provide le possibilitate de comparar le configurationes de columnas de fractionation de succo gastric obtenite sub varie conditiones e in varie statos pathologic. Observationes preliminari indica que le succo gastric de patientes con dystrophia myotonic es forsan distinguite per le absentia de certe proteinas que es presente in le succo ab individuos normal.

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RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(ELEVENTH RHEUMATISM REVIEW) *

Part I

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Definition of "Rheumatism" and "Rheumatic Diseases"

These terms have been used to embrace a large and miscellaneous group of diseases and disorders of the supporting tissues, including all types of arthritis, rheumatic fever, a large and poorly defined group of disorders primarily non-

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The last Review prepared by the Editorial Committee of the American Rheumatism Association was the Tenth; it concerned the American and English literature from 1946 through 1950, and was published in the Annals of Internal Medicine, Volume 39, September and October, 1953. This Eleventh Review is concerned with the literature from 1951 through 1953. The editorial comments express the opinion of the authors of the Review, the Editorial Committee, and are not necessarily those of the Association.

articular or extra-articular in distribution, and the diffuse diseases of collagen-containing tissue such as periarteritis nodosa, lupus erythematosus disseminatus, dermatomyositis and scleroderma.[408]

Though the term "arthritis" had been used in Hippocratic times, the word "rheumatism" was introduced by Galen 1800 years ago to indicate pain resulting from a discharge of peccant humors into body cavities (Rheuma—a flux). Thus, any discharge into a body cavity or surface was labeled "rheumatic," and of these arthritis was but one; others included pleurisy, pericarditis, meningitis, and even nasopharyngeal catarrh. This "dropping" into a joint cavity gave the name "gout" (gutta—a drop) to any form of arthritis until Sydenham, and later other natural historians of disease, were able to separate entities showing distinctive clinical features from amongst the broad group of "rheumatic" disorders. Gradually the term "rheumatism" began to be limited to painful diseases of the locomotor system, joints, muscles, fascia and bone.[388] An interesting historical commentary on trends in treatment of rheumatic diseases was recorded.[760]

General Incidence of Rheumatic Diseases

Social and Economic Importance

It was estimated that about 2,000,000, or 4%, of the population of the British Isles,[794] and about 7,500,000, or 5%, of the population in the United States[988] suffered from some type of "rheumatic" disability. In Denmark the morbidity due to rheumatoid arthritis over the five-year period from 1947 to 1952 was calculated as 0.8 per 1,000—that is, about 3,000 to 4,000 of Denmark's 4,500,000 inhabitants were liable to be attacked by this disease each year.[37] The economic impact of rheumatic diseases was further emphasized by statements that they caused nearly one sixth of the total industrial invalidism in England and Wales, with an annual work loss of 3,000,000 man-weeks. Seventy per cent of victims of the more disabling types were under 55 years of age, when they should be at their optimal productive activity.[388] It was pointed out that, in the United States, arthritis and rheumatism caused more years of disability than did all types of accidents.[988] In one American industry with 25,000 employees, 4,200 work days were lost each year due to rheumatic disorders,[302] and the total annual loss from this cause in the United States was estimated as 97,200,000 days, with an approximate cost of 100 million dollars per year for medical care alone.[408] The inadequacy of medical records and statistics on rheumatic disorders in industry was demonstrated, and technics for improved recording were recommended to industrial physicians.[302, 679] An appreciable mortality due to rheumatoid arthritis was emphasized by statistics from the British Ministry of Health.[276]

Difficulties in the collection and interpretation of statistics regarding the prevalence of these diseases were wisely stressed.[388] But both extensive and intensive surveys yielded more accurate information than had previously been available, and indicated methods by which the two types of surveys might supplement each other. From a survey of 25,000 households scattered through 68 sample areas in 42 states it was estimated that there were about 10,104,000 persons 14 years of age and over in the United States who believed they had arthritis or rheumatism. This constituted 9.3% of this portion of the popula-

tion. About 75% of these had consulted a doctor about their rheumatic complaints. An estimated 6,404,000 (5.9% of the population) had been told by a doctor that their condition was arthritis, rheumatism, gout, lumbago, myositis or fibrositis. [This survey excluded data on rheumatic fever.—Ed.] About 25% of the 10,000,000 had made some significant change in the type or amount of work they performed or in their usual activities because of their "rheumatic" disability.[2290] "When the age factor is also considered, the economic ramifications of this public health problem are clearly illustrated. Because of some form of arthritis or rheumatism, 1.5 to 5% of the population in the age group of 45 to 60 years are forced to stop work entirely, change to part-time or occasional work, or make some other significant alteration in their employment or other usual activities."[1930] [This survey in September, 1951, provided the first estimate of the prevalence of arthritis and rheumatism in the United States since the National Health Survey of 1935–36. It was conducted in a carefully designed sample representative of the population of the country, permitting definition of limits of error due to sampling. It was a questionnaire type of survey, but answers were obtained by interview. It is emphasized that information was obtained by lay respondents, reporting what they believed the doctor had said. Only by linking such surveys with studies using more intensive screening and diagnostic methods—of necessarily much smaller groups—will an estimate be possible of the number of persons with unquestioned arthritis of each type. "The survey of September, 1951, will therefore be useful as a means of calibration, provided the identical questions used in the national are also incorporated into the smaller surveys to provide the link."[2290]—Ed.]

Such an intensive survey was reported in a sample of the general population of a Lancashire town.[1131] In this study, all patients having rheumatic complaints at the time of interview were appraised by a physician, and some subjects received thorough physical and x-ray examination. Forty per cent of those interviewed stated that they had had some "rheumatic" complaint at some time in their lives, and about 19% had "rheumatic" symptoms at the time of the survey. Nearly half of those with such complaints had never consulted a doctor, and only one fifth had ever been hospitalized or had attended out-patient clinics. [This emphasizes the fallacy of calculating rheumatic disease incidence on the basis of records from physicians' offices, hospitals and clinics.—Ed.] Of 1,007 working individuals, 340 had been off work for one week or more, and 139 had lost three months or more. It was observed that even rheumatoid arthritis was not always a severe, crippling disease, and half the individuals with this disease had lost no working time in the preceding five years. This mild course of some cases of rheumatoid arthritis was also noted in a Danish survey.[37] It was pointed out that these figures might not be applicable as an index of incidence throughout England but, when compared with previous British studies, the incidence of total rheumatic complaints was similar. In a study of rheumatism in miners, Lawrence and Aitken-Swan[1248] and Kellgren and Lawrence[1130] found a gross incidence of rheumatic complaints similar to that in the nonmining population, but there was evidence of an earlier onset in the miners, chiefly due to an increased incidence of degenerative disc disease in the lower spine and to osteoarthritis. Loss of working time due to rheumatic complaints was greater among miners than in the general population; in fact, these disorders were the second most frequent cause of invaliding from the mines. It was estimated that if all miners suffering from rheumatic disorders could be cured, coal production in the British Isles could be doubled.[794]

Classification of Diseases of Joints and Related Structures

The obscure nature of many of the "rheumatic" disorders continued to make it difficult to produce an entirely satisfactory classification of this group of diseases. The classification adopted as official by both the American Rheumatism Association and the Standard Nomenclature of Disease was recorded in detail in the Ninth Rheumatism Review, the American Rheumatism Association's *Primer on the Rheumatic Diseases,*[408] and in the Arthritis and Rheumatism Foundation's *Manual for Arthritis Clinics,*[68] where detailed criteria for each diagnosis were also described. Minor modifications of this classification were also recorded.[388, 988]

Relative Frequency of the Rheumatic Diseases

The relative frequency of the rheumatic diseases, as estimated on the basis of patients attending arthritis clinics and rheumatism centers, varied greatly.[83, 408] More meaningful were the results obtained on medical interview of a sample of the population of a Lancashire industrial town[1131] (table 1). It was found that among the miners, disorders of intervertebral discs in the lower spine (degeneration and prolapse) were the most common rheumatic disability, osteoarthritis was the next, and rheumatoid arthritis was uncommon. Among the females of the miners' families, osteoarthritis was the most common, rheumatoid arthritis occurred much more frequently than among the males, and disc disorders were rare.[1130, 1248] In a study of rheumatic complaints in an American corporation with 25,000 employees, 37% of the disabilities were due to osteoarthritis, 13% to bursitis, 11% to gout, 8% to rheumatoid arthritis and spondylitis, and 31% to other rheumatic disorders difficult to classify because of inaccurate recording.[302] [All surveys will remain limited in value and be difficult to compare until uniform diagnostic criteria for the various rheumatic diseases are established and are generally accepted.—Ed.]

TABLE 1

Rheumatic Complaints at the Time of Interview and Over the Prior Five Years
(After Kellgren, Lawrence, and Aitken-Swan[1131])

	At Time of Interview 2,898 Individuals Interviewed		Over Prior 5 Years 3,515 Individuals Interviewed	
	Number of Patients	Per Cent of Those Interviewed	Number of Patients	Per Cent of Those Interviewed
Osteoarthritis	185	6.4	277	8.0
Rheumatoid arthritis	70	2.5	109	3.0
Rheumatic fever	9	0.3	22	0.6
Gout	2	—	6	0.2
Other forms of arthritis	4	0.1	5	0.1
Ankylosing spondylitis	1	—	2	—
Disc degeneration and prolapse	79	2.7	174	5.0
Bursitis and synovitis	11	0.4	41	1.2
Other diagnosable disorders	6	0.2	21	0.6
Undetermined	155	5.3	395	11.3
Entirely psychogenic	2	—	7	0.2
Not seen by physician	17	0.6	102	3.0
Total	541	18.5	1,161	33.2

Diseases Related Primarily to Trauma

Lesions Produced by Acute Trauma. Trauma can produce a variety of lesions, varying from the simplest (a "strain") which recovers rapidly, to the more severe injuries, such as a sprain, synovitis, hemarthrosis, dislocation, fracture or traumatic arthritis. A sprain represented actual disruption of the supporting structures of the joints and involved tears of ligaments, joint capsule, blood vessels, cartilage or nerves.[886, 2003] Acute trauma most frequently affected the knee and the ankle joints. The knee was the most vulnerable joint (because of anatomic structure and the variety of stresses to which it was subject), and trauma to it frequently involved tears of the collateral or the anterior cruciate ligament, injury to the medial meniscus, or fracture of lateral condyle of tibia.[340, 1946, 1974, 2003]

Traumatic synovitis resulted from damage to the synovial membrane, but effusion did not occur until six to eight hours after injury and required aspiration only when severe. Hemarthrosis was indicative of more severe injury to the quadriceps apparatus or the collateral ligaments; it appeared within one hour and required aspiration.[323, 505, 886, 1946] The presence of fat in the synovial fluid after severe trauma indicated an intra-articular fracture.[886]

Joint wounds were best treated by thorough debridement, removal of all foreign bodies or damaged articular tissues, excision of the patella if shattered, irrigation with normal saline, closure of the joint capsule plus instillation of penicillin. When joint damage was severe and ankylosis was probable, immobilization in the position of optimal function was indicated.[370] In seven children reported from California, palm thorns served as a foreign body irritant to produce joint effusion persisting after associated infection was controlled by antibiotics. The knee was most often involved, and a history of penetrating injury was usually not obtained.[1106]

Both phenylbutazone and intra-articular hydrocortisone were reported as producing major improvement in traumatic arthritis.[823] [Again, most authors failed to specify whether by this term they were dealing with (a) immediate results of acute trauma, (b) late results of a single traumatic episode, or (c) the results of minor repeated trauma.—Ed.]

Late Results of Trauma. Repeated minor trauma or the failure to recognize the precise nature of acute trauma often resulted in chronic disability, joint instability or secondary osteoarthritis. In the case of wrist "sprain" it was necessary to take oblique x-rays to rule out navicular fracture, which could lead to non-union, aseptic necrosis and osteoarthritis.[370, 1974, 2003] Failure to recognize or to institute proper treatment for a severe injury resulted in joint instability or arthritis of the ankle[530, 1974, 2003, 2124] and of the knee.[340, 505] An acute injury or repeated trauma resulting from excessive use of the arm in abduction was believed to produce injury to the rotator cuff of the shoulder, leading to bicipital tenosynovitis or calcareous tendinitis. A "frozen shoulder" or weakness of abduction was a not infrequent complication.[505, 2003] [Many workers do not agree that trauma is an important factor in the "painful shoulder".—Ed.]

Special Locations. *Temporomandibular Joint.* The gross and radiographic anatomy and the physiology of this joint, as well as the etiology and pathology of its derangements, were thoroughly reviewed.[149, 175, 621, 1160, 1650] Forty per cent of 1,200 unselected patients had subluxation due to abnormal occlusion of the teeth.[124] Most

of the acute traumatic, arthritic or inflammatory lesions of the joint responded to conservative treatment. In acutely painful joints this treatment included cold applications, sedation, immobilization of the jaw, and antibiotics when indicated for infection; later, heat, motion, and orthodontic appliances were employed.[149, 525, 621, 1160] Chronic internal derangement of the joint, producing locking or severe pain, was successfully treated by meniscectomy.[149, 524, 525, 621, 1160] Ankylosis was treated by resection of the condyle and also the coronoid on one or both sides, plus plastic surgery to correct facial deformity when necessary.[1650] Injections of sclerosing agents were used only for hypermobility of the joint.[149]

Patella: Chondromalacia and Osteoarthritis. Chondromalacia patellae was believed to result from recurrent local injuries to the articular surface in young males. [It is doubtful that recurrent trauma is the only cause.—Ed.] X-ray examination may be negative until loose bodies are present. If conservative treatment by physical therapy and temporary immobilization of the knee was not successful, surgical excision of disintegrated cartilage, patellaplasty, or excision of the patella was advised.[340, 1500] Recurrent subluxation of the patella was considered the probable diagnosis in women suspected of internal derangement of the knee. While minor degrees of subluxation were corrected by redeveloping the vastus medialis, severe cases required surgical transplanting of the tibial tubercle with the attached patellar tendon to the medial aspect of the tibial head.[1946] Focal degeneration of the patellar tendon in three patients was believed to have been caused by excessive use of the leg. Conservative treatment (heat, rest, and possibly novocain injections) was recommended, although the condition was diagnosed by surgical exploration.[1465]

Two patients with internal derangement of the knee were relieved by excision of the fabella, which demonstrated degenerative changes on the articular surface ("chondromalacia fabellae").[787]

Knee—Internal Derangements. The most frequent injury in "knee sprain" was a tear of the medial collateral ligament, which often involved the attached medial meniscus.[2003] The usual mechanism was a blow on the lateral side of the knee, or a "twisting force" at the knee when the leg was bearing weight.[340, 1974] The common signs of semilunar cartilage injury (usually the medial meniscus) were recurrent pain in 97%, "locking" in 70%, and swelling in 95% of patients.[340] Failure to recover full extension of the knee after procaine infiltration of the tender ligaments suggested injury to the meniscus.[323] If extension after acute injury was accomplished by gentle manipulation under anesthesia, conservative treatment by early immobilization followed by quadriceps setting exercises was successful. When the knee remained locked, or recurrent attacks of pain, swelling and locking occurred, surgical excision of the damaged meniscus was indicated. Incomplete ligamentous tears were best treated by cold, immobilization for six to eight weeks until stability was regained, and quadriceps rebuilding exercises as soon as possible. When the diagnosis of a complete tear of the collateral or cruciate ligament was possible, early surgical repair was indicated.[340, 1500, 1946, 1974] Rupture of the quadriceps tendon demanded immediate surgical repair, but the uncommon rupture of the patellar tendon was treated by immobilization for six weeks with the knee in extension.[340] All agreed that quadriceps rebuilding exercises were vitally important in the rehabilitation of the knee after any type of severe injury, whether or not surgery was necessary.[2, 340, 1500, 1794, 1946, 1974]

Some considered that cysts of the menisci were the result of degenerative processes.[1414] Others thought that they arose from developmental inclusions of synovial cells within the semilunar cartilage, and that actual cyst formation might be excited by injury or even by normal use of the joint.[201] There was agreement that such diseased menisci, when responsible for symptoms, should be excised.[340, 1946, 2003]

Contrast radiography with air [918, 2006] and with a double contrast method utilizing both an opaque dye and oxygen [1603] were considered valuable diagnostic procedures

for the many pathologic lesions of the knee joint. Others [1079] considered arthrography a valuable supplement to the clinical examination only when performed with certain definite indications. Careful study of routine x-ray films under spotlight illumination was believed to yield as much information about soft tissue pathology as the more difficult contrast studies of the knee.[1285]

"Pellegrini-Stieda Disease." A sprain or partial avulsion of the medial collateral knee ligament from the femoral attachment was believed to result in calcification characteristic of this condition. Recommended treatment consisted of infiltration with local anesthetics, use of an elastic compression bandage, and avoidance of massage, passive motion or manipulation. If disability due to loss of flexion occurred, excision of the bony mass was advised when the lesion was quiescent.[1046]

Sprains and Strains. The diagnosis of "sprain" frequently masked a more serious injury, especially to the ankle, wrist or fingers. The term should be used to include the syndrome of swelling, pain and muscle spasm which accompanies all injuries to joints, and careful examination should be carried out to determine which anatomic structures have been damaged.[405] Severe "sprain" of the ankle was frequently a disruption of the talofibular ligament, "occult" dislocation, or "sprain fracture." Special x-rays of the ankle in forced inversion or eversion, after local or general anesthesia, were required to diagnose complete tears of the talofibular ligament or subluxations. Such complex injuries required immobilization in plaster for periods of up to six weeks to prevent chronic instability or arthritis of the joint.[323, 530, 1974, 2003, 2124] Less severe injuries were treated successfully by ethyl chloride spray and an elastic bandage,[1687] or by a sural nerve block.[1033] Local anesthesia was used for diagnosis but was not condoned for treatment.[495, 1974, 2124]

The "baseball" or "mallet" finger resulted from avulsion of the extensor tendon and a chip fracture at the site of its attachment to the distal phalanx. This injury was treated by immobilization for from six to eight weeks, with the distal joint in hyperextension and the proximal joint in flexion.[443, 1974]

"Tennis Elbow" (Radiohumeral Bursitis). This syndrome of pain in the region of the lateral epicondyle extending down the dorsilateral aspect of the forearm occurred in patients as a result of "heavy" occupational use of the elbow or frequent pronation-supination movements of the extended elbow.[796, 1494, 2020] Several pathologic lesions were believed to produce the syndrome: incomplete tears of the extensor muscles from their origin at the lateral epicondyle,[2020] repeated pinching or a tear of the synovial membrane,[1493, 1494] and also radiohumeral bursitis or a tear of radiohumeral ligament.[1493]

Furlong [718] regarded this as a self-limited condition, with spontaneous cure occurring in about nine months. Local injections of procaine [796] or hydrocortisone [2020] into the tender areas were usually effective, plus splinting and physical therapy in some patients. Excision of the thickened synovial fold was performed successfully in 16 patients,[1493] and was recommended when conservative treatment failed.

Secondary Influence of Trauma on Joint Disease. Some believed that trauma could be a precipitating factor in rheumatoid arthritis, particularly determining localization of the joint inflammation, in patients in whom the "constitutional factor" also was present.[1137] Kelly reviewed studies on the relationship of trauma to rheumatoid arthritis, and reported 32 patients in whom mono-articular pain and swelling appearing immediately after injury persisted until other joints were involved. The interval before arthritis appeared in other joints ranged from one week to two years; it affected the opposite joint in 13 patients, and two symmetric joints in 12.[1136] In 118 patients with "ankylosing spondylarthritis," nine dated the onset of their symptoms from an episode of severe trauma to the lower back.[811] [Evidence that trauma contributes significantly to the onset of rheumatoid arthritis or rheumatoid spondylitis remains unconvincing.—Ed.] The ability of trauma to precipitate an acute attack of gout was again noted.[136]

A new concept, "traumatic arthrofibrosis," was suggested to explain severe, protracted changes in either an injured joint or adjacent soft tissues that resulted in irreversible damage or fibrous ankylosis. The lesion was most common in the hip and knee, and appeared to be aggravated by prolonged immobilization. While it was thought possible for it to follow mild trauma, it was most often a complication of intra-articular fracture. Destruction of cartilage resulted from pannus formation and cellular action. Biopsies revealed no evidence of the usual degenerative or inflammatory response. The histologic picture was that of fibroplasia with edema and hyperemia but no focal or diffuse round cell infiltration.[1336] [This concept is vague and does not provide a basis for the differentiation of any group of cases.—Ed.]

Arthritis Due to Specific Infectious Agents

The remarkable advances of antibiotic and chemotherapeutic measures in controlling infection were reflected in a decreasing literature dealing with arthritis due to specific infectious agents. No articles dealing with syphilitic arthritis, dysenteric arthritis, or arthritis associated with lymphopathia venereum or granuloma inguinale were encountered. [Charcot's joints are discussed under the section on neuropathic arthropathies.—Ed.] Meningococcal arthritis received only passing mention.[33, 2035] A single case of typhoid spondylitis, successfully treated with chloramphenicol, was reported.[483]

Gonorrheal Arthritis

While genital gonorrhea continued to occur at a high annual rate, gonorrheal arthritis has become a disappearing disease.[554] In the only clinical report concerned exclusively with gonorrheal arthritis, the interval between genitourinary infection and the onset of joint symptoms was less than four weeks in 15 of 30 patients. In 24 of 30 patients the joint involvement was migratory at the onset, and only four patients developed persistent mono-articular involvement. Thirteen patients in this series developed arthritis in spite of previous penicillin or sulfonamide therapy.[870] Gonococcal arthritis was believed to produce more advanced stages of fibrosis and ankylosis than other types of suppurative joint disease; cartilage destruction was most extensive in the hip and ankle joints.[2035]

The theory was stated that the cause of arthritis in gonorrhea was the same as in the arthritis of nonspecific urethritis and Reiter's syndrome. In a group of 106 patients with arthritis and urethritis, only 44% had gonorrheal urethritis, yet no clinical differentiation was possible between patients in whom gonococcal infection was present and those in whom it was absent. The triad of symptoms (arthritis, urethritis and conjunctivitis) known as Reiter's syndrome was observed in 19 patients, and keratodermia blennorrhagica in 32 patients.[1280] Similar views were expressed concerning another group of 21 patients, only nine of whom had gonococcal urethritis. It was believed that there was a form of arthritis related to venereal urethritis and distinct from rheumatoid or gonorrheal arthritis. This form usually consisted of self-limited attacks of from one to 12 months' duration, but recurrences or chronic arthritis produced residual deformities of the feet (11 patients) and ankylosing spondylitis (four patients). Eye complications (iritis, conjunctivitis) were frequent, and keratodermia occurred in some.[670] [It appears that some of these patients reported presumably had Reiter's syndrome. More evidence is necessary to warrant the designation of a new symptom complex of "venereal arthritis." Acute arthritis associated with urethritis

may be gonorrheal arthritis, rheumatoid arthritis, or the arthritis of Reiter's syndrome.—Ed.]

Diagnosis. The necessity of demonstrating the presence of the gonococcus in joint fluid for a positive diagnosis of gonococcal arthritis has been emphasized in previous reviews. In only one report was there specific mention of this fact; gonococci were found in the joint fluid of five of their 30 patients.[870] In another series of 70 patients with acute purulent arthritis, the gonococcus was identified as the responsible organism in 25.[33] The gonococcus complement fixation test was positive in 24 of 30 patients and was thought to be a valuable diagnostic procedure.[870]

Treatment. It was generally agreed that penicillin is the preferred treatment for gonococcal arthritis. Twenty-two of 24 patients[33] and 27 of 30 patients[870] had satisfactory results. Three apparently penicillin-resistant patients responded to Aureomycin and streptomycin, fever therapy, and fever therapy plus streptomycin, respectively.[870]

Those who held that "venereal arthritis" was not related to gonorrhea found hyperthermia and fever produced by intravenous injections of typhoid antigen to be effective, while sulfonamides and streptomycin were used in some patients, with questionable results.[670, 1280] Phenergan was of value in three patients,[1280] while cortisone and corticotropin produced only temporary suppression of the arthritis.[670] [The paucity of reports of proved gonococcal arthritis bears mute testimony to the efficacy of penicillin in the elimination of gonococcal infection of the genitourinary tract.—Ed.]

Keratodermia Blennorrhagica. Clinical observations continued to challenge the specificity of this skin lesion as a complication of gonorrheal arthritis. The difficulty in distinguishing it from rheumatoid arthritis with pustular psoriasis was again illustrated.[1328] It was suggested that keratosis blennorrhagica was a "reaction pattern" similar to the tuberculid reaction, since one patient responded to corticotropin therapy after various other treatments, including penicillin, broad spectrum antibiotics and typhoid vaccine, had failed.[1523] [The gonococcal etiology in this patient is open to serious question.—Ed.] However, in a second patient, in whom genital gonorrhea was proved, penicillin effectively suppressed the joint manifestations without significant effect on the skin lesions. Subsequent use of corticotropin was followed by prompt improvement and eventual clearing of the keratodermia.[1881] Autopsy findings were reported in one patient with ankylosing arthritis and keratodermia of three years' duration. Joint involvement occurred four to five days after presumed but not proved gonorrheal urethritis, and skin involvement nine weeks later. Both joint and skin lesions progressed despite treatment with sulfonamides and antibiotics.[2063]

Tuberculous Arthritis

There has been a tremendous decrease in the incidence of bone and joint tuberculosis in the past 30 years, attributable to such preventive measures as the control of food supplies, segregation and better treatment of tuberculous patients, and education of the general population.[240, 749]

Clinical Data. The factors that determine the outcome of patients with bone and joint tuberculosis were reviewed.[240] The prognosis depended upon the amount of general involvement rather than upon the extent of the osseous

lesion itself.[240, 274, 534] Search for tuberculous lesions in 75 patients with sacroiliac tuberculosis disclosed that 83% had tuberculous lesions elsewhere.[1975] Patients with pulmonary involvement had the poorest prognosis.[240, 241, 274] Multiple lesions of bone were observed in 10% of 172 tuberculous children.[1479] One patient with coexisting tuberculosis and coccidioidomycosis of the same bones was believed to be the first case reported.[686]

Diagnosis. Soft tissue changes and shadows were more important to early x-ray diagnosis than x-ray changes in the bone.[240, 1245] Diagnosis should be established by every possible method; aspiration or open biopsy is no longer feared, because antibiotics now prevent such complications as draining sinuses.[181] Exploration, with biopsy and guinea pig implantation of excised tissues, was advised even though the tuberculin test was negative.[241] Punch biopsy of the synovial membrane confirmed the diagnosis of tuberculosis in nine of 10 patients.[1671]

Special Locations. *Spine.* Spondylitis remained the most common osseous involvement of tuberculosis. It constituted 50%[1693] and 47%[1294] of cases of bone tuberculosis. Evidence of destruction of the vertebral plate or the intervertebral disc, especially in the anterior portion, or a fusiform paravertebral shadow, was helpful in early diagnosis,[181] but definite differentiation between chronic pyogenic and tuberculous spondylitis depended on the demonstration of the tubercle bacilli.[34] It was advised that a stable arthrodesis be obtained as soon as possible. When a firm arthrodesis was secured, 80% of paraplegic patients recovered.[181, 241]

Hips. Tuberculous involvement of the hip comprised 24% in one group[1693] and 14% in another series of osseous tuberculosis.[1294] It was dangerous in young children because of the insidious onset and the difficulty of diagnosis. The triad of pain, limp and deformity did not occur early,[1245] and the disease was present for an average of 10 months before diagnosis in one series of 320 patients, with widespread destruction in 101.[534] X-ray tomography was recommended to obtain accurate information as to degree of joint integrity, and to define areas of necrosis or cavitation.[2283]

Immobilization of the hip joint and correction of deformity by traction or by splints were helpful, in addition to the use of streptomycin and para-aminosalicylates (PAS). Surgical procedures were used later when the disease was inactive.[1245] A stable ankylosis developed in 46% of 173 patients treated by conservative means, and in all of 97 treated by arthrodesis or osteotomy. Failure to obtain a stable arthrodesis was followed by deformity or reactivation of the disease.[534] Once fusion has occurred, no attempt should be made to mobilize the joint because of possible reactivation.[241] Streptomycin and PAS therapy arrested tuberculous hip disease in two patients.[895]

Knees. In tuberculosis of the knee joint there was less likelihood of osteocartilaginous damage, and there were a few reports of patients apparently cured by streptomycin and PAS without surgical treatment.[181, 895, 1959] Four of 10 patients with synovial tuberculosis apparently recovered after a course of intra-articular injections of streptomycin.[13] In the prechemotherapeutic era, surgical resection of 369 knees produced ankylosis in 83%, and 96% were eventually able to work.[274] In one patient, extensive knee joint disease healed with complete restoration of function after immobilization in plaster for over two years.[1194]

Trochanter and Bursae. Tuberculous trochanteric bursitis was reported in 35[1294] and in eight patients.[1985] The underlying bone was involved in some. Their symptoms were dull pain, fluctuant swelling, or sinus formation. Tuberculosis of olecranon and ischial bursae with no bony abnormality was reported,[1985] but in some patients with subdeltoid and subscapular bursitis the contiguous bone was involved.[1141, 2107]

Treatment consisted of excision of the bursa and infected tissue, including bone,[1141] plus streptomycin and PAS.[1985]

Other Joints. Sacro-iliac tuberculosis was reported in 75 patients, usually young adults, and was bilateral in seven. Involvement of the spine in 22 and the hip in 10 patients suggested that the psoas muscles served as a channel for the spread of infection. Operative fusion appeared to hasten a satisfactory result.[1975] Tuberculosis of the ribs and symphysis pubis was reported.[241]

Treatment. Streptomycin combined with PAS made early and safe surgery possible. Early eradication of sinuses and abscesses was possible with primary healing of closed wounds. Use of these drugs practically eliminated local recurrences or sinus formation and decreased the incidence of tuberculosis elsewhere in the body. Often they permitted restoration of joint function. Early synovial tuberculosis was arrested in some patients by drug therapy alone.[23, 33, 181, 241, 242, 511, 629, 749, 895, 970, 1245, 1293, 1294, 1479, 1590, 1591, 1594, 1693, 1959, 1985, 2004] The dosage and length of administration of streptomycin and PAS varied considerably. Most authors employed streptomycin, 1 gm., with 10 to 12 gm. of PAS daily for periods of about three months. Smaller doses of streptomycin, 1 gm. twice weekly, and PAS, 4 gm. daily for two to three months,[629] and even courses of streptomycin for 14 days only, were used with apparent success.[1590, 1591] Bosworth administered much larger amounts of streptomycin, and emphasized that the deafness which occurred in 5.8% of his patients was an acceptable complication when one considered the record of salvage from tuberculosis. Streptomycin reduced mortality by 65.3% on all services and by 80% on the orthopedic service.[242]

Studies of blood and synovial fluid levels of streptomycin indicated that this drug readily passes into and out of the synovial cavity. High levels of the antibiotic persisted in the joint fluid for 10 hours after its intramuscular administration, and persisted as long as 24 hours after intra-articular injection. With intramuscular administration, tuberculostatic levels were found in the pus in 14 of 22 cases of bone tuberculosis with abscess formation.[644]

In the few reports available, the isonicotinic acid hydrazides produced marked improvement in the tuberculous bone and joint lesions, as well as in the general health of the patient.[243, 296] After 14 months' experience with iproniazid in 66 patients, one group felt that this was the drug of choice, despite a high incidence of toxicity.[244]

It was agreed that surgery still had a very important place in treatment. Drainage of abscesses, excision of sequestra, excision of sinuses or other infected tissue, and arthrodesis of the spine should be performed as soon as possible.[23, 33, 241, 242, 274, 511, 629, 749, 970, 1141, 1245, 1293, 1294, 1479, 1590, 1591, 1594, 1959, 1985, 2004] Stabilization of damaged joints should be postponed until conservative therapy has been tried and until there has been time to reëstablish a normal epiphyseal plate in children, or until the disease is inactive.[181, 511, 1245] The combination of general sanatorium measures, antibiotics and chemotherapeutic measures, and surgical removal of necrotic foci, with or without partial synovectomy, was successful in 20 of 23 cases of spinal involvement, in 19 of 23 tuberculous hips, and in 14 of 16 tuberculous knees. "In children with tuberculosis of the hip, and in adults and children with tuberculosis of the knee, it is usually possible to save the joint and restore function, provided the joint has not been destroyed before

treatment is begun."[2250] The need for longer follow-up observation to evaluate the risk of recurrence was emphasized.[1590]

Tuberculous Rheumatism (Poncet's Disease)

One additional patient was reported with an acute rheumatoid type of polyarthritis, followed by probable tuberculous arthritis of one hip which responded to traction, streptomycin and PAS. The polyarthritis subsided quickly; it was thought to have been caused by sensitization to the tubercle bacillus.[476]

Suppurative Arthritis

The pathologic characteristics of pyogenic arthritis were reviewed in 352 patients with septic arthritis. In streptococcal and staphylococcal infections, actual suppuration did not occur until the third or fourth week, when great damage to the cartilage resulted. In the pneumococcal type, cartilage destruction was not so extensive and recovery was not unusual, especially in children. The hip was the most frequently involved joint in children; the knee and the joints of the upper extremity were more common sites in adults. The earliest diagnostic signs were tenderness and pain, rather than redness, heat or swelling. X-ray evidence was a late manifestation unless there was a neighboring osteomyelitic process.[2035] Occurrence of septic arthritis of the hip in early infancy,[952] and the difficulty in differentiating this from a benign transient synovitis,[552] were again noted.

Septic arthritis was frequently caused by hemolytic *Staphylococcus aureus* as a result of direct extension from a nearby osteomyelitis in children.[327] In 70 patients with suppurative arthritis, the staphylococcus was isolated in 29, the gonococcus in 25, the pneumococcus and meningococcus in three each, hemolytic streptococcus and *Hemophilus influenzae* in two each, and paracolon bacillus and *Aerobacter aerogenes* in one each; cultures were sterile in four. In this series of patients the knee was involved in 40%, the hip and the ankle each in 15%.[33] Aspiration of the joint was recommended for diagnosis and determination of bacterial sensitivity so that early and adequate antibacterial therapy could be given.[33, 327]

Treatment. Penicillin was used successfully in the majority of suppurative joint infections, although Terramycin, Aureomycin and chloramphenicol were sometimes employed as a result of bacterial sensitivity tests. Excellent results were obtained in 62 of 70 patients.[33] In addition to antibacterial therapy, immobilization and early drainage of the joint were considered essential if pus was present (especially in the hip) to prevent extensive joint damage.[1025, 1245, 1947, 2035] Evacuation of the joint was determined by the nature of exudate and type of organism. Simple aspiration usually sufficed in streptococcal infection, but rapid evacuation was important in staphylococcal infection, at times necessitating open drainage.[2035] Reconstructive joint surgery (arthroplasty, osteotomy or arthrodesis) was performed only after absolute quiescence of joint inflammation.[1245, 1947, 2035]

Brucellosis

Incidence and General Clinical Data. Prevention of human brucellosis again emphasized the control of the disease in animals. Great progress has been

made by controlling bovine brucellosis and by adequate heat treatment of cow's milk and milk products, particularly in reduction of human brucellosis due to *Brucella abortus*. There was increased cross-infection of the various species of brucella among domestic animals and danger of transmission of *B. melitensis* to humans.[2292] Direct contact with infected animals was responsible for the majority of brucella infections, rather than ingestion of contaminated milk products.[512, 1996, 1997]

In both experimental and clinical infection, *B. melitensis* produced the most severe disease, *B. suis* caused suppurative lesions, and *B. abortus* produced the least severe infection.[260, 1996] Accidental infection by strain 19 was reported in two veterinarians, and this organism was recovered for the first time from the blood of a human with brucellosis.[1999] Two patients with apparent acute "reinfection" were reported.[827]

Brucellosis was regarded as a form of intracellular parasitism in which brucella organisms localized and even multiplied within the phagocytes of the reticuloendothelial system and were protected from the action of antibiotics.[260,1996] The spleen, while not essential for defense against brucella, was found to protect the liver from invasion by the organisms.[261, 262]

Spink[1996] attempted to answer questions concerning the existence and nature of "chronic brucellosis" by following the natural course of the disease in 65 patients with active brucellosis. The illness was prolonged for more than one year in 30 patients; in five this could be explained by clinical and laboratory evidence of relapse, and 12 had evidences of a localizing complication. In the remaining 13 patients, subjective complaints of ill health persisted despite absence of objective evidence of active brucellosis. "With almost monotonous regularity they complained of weakness, vague aches and pains, easy fatigability, nervousness and mental depression." In 11 of these 13 there was evidence of emotional instability or severe psychoneurosis. Spink concluded that the diagnosis of chronic brucellosis is on very uncertain ground if based on subjective complaints only, a positive skin test, and absent or low titer of brucella agglutinins.[1996] Others defended the concept of chronic brucellosis as a disease with mild onset, an undulating clinical course characterized by a fairly constant substrate of debility and discomfort, rarely manifesting hyperpyrexia and bacteremia; symptoms were attributed to an allergy to the entrenched brucella, and the disease was stated to respond characteristically to specific vaccine therapy.[844, 845] [No longer is it seriously claimed that brucellosis is responsible for rheumatoid arthritis or osteoarthritis.—Ed.]

Symptoms Referable to Joints and Muscles. Arthralgia, backache, pain along the spine, and vague aches and pains were common.[512, 943, 1996, 1997] In one series of 94 proved acute cases, backache occurred in 51% and arthralgia in 44%.[1998]

Localized Bone and Joint Lesions. Spondylitis was the most frequent complication, occurring in one study in nine of 126 patients.[1996] It resembled tuberculous spondylitis, with the exception that recovery was relatively rapid.[1169, 1996] Hip joint involvement dominated the clinical picture of acute brucellosis in two patients;[169, 575] transient manifestations in other joints were noted, and polyarthritis of the serous type was stated to be more frequent than involvement of a single joint.[2035] Sacro-iliac involvement,[1998] suppurative arthritis of the hip, elbow, knee and shoulder,[943, 1998, 2217] osteomyelitis[943, 2217] and suppurative

bursitis[2217] were recorded. It was emphasized that the brucella organism may be isolated from excised tissues when there is no obvious history or clinical course to suggest brucellosis, and that the gross and microscopic appearances of the lesion may be nonspecific, or may be strikingly similar to those of tuberculosis.[2217]

Diagnosis. Culture of brucella was the most certain method of diagnosis; this was most often obtained from blood or bone marrow.[943, 1166, 1360, 1996, 1997, 2292] Positive cultures have also been obtained from other body fluids, abscesses, sinus drainage and surgically removed tissues.[1997, 2217, 2292] Special culture media and precautions favoring recovery of the organism were described.[47, 1996, 1997, 2217, 2292]

The serum agglutination test, when carried out with a suitable antigen and by a satisfactory technic, almost always gave significantly positive results in the presence of active brucella infection. A high or rising titer (1:100 or more) in the presence of symptoms was valuable evidence of brucella infection.[478, 1996, 1997, 2292] In areas where brucellosis was endemic, caution was advised in interpreting low agglutination titers in patients with ill-defined symptoms. Positive agglutination titers have been produced by cholera and tularemia, or by immunization against these diseases.[2292] Agglutination tests were particularly valuable when prior use of antibiotics had made it difficult to obtain positive cultures. Modifications of the agglutination reaction were described which were believed to be more sensitive[647] or more rapid.[1818] The intradermal test was not diagnostic of active infection, and the complement fixation and opsonocytophagic tests were not recommended for routine use.[1996, 1997, 2292]

Treatment. All authors emphasized that ideal antibiotic or chemotherapeutic eradication of the disease had not been achieved, and that relapses had occurred after the use of all agents.[2292] Spink, dealing chiefly with *B. abortus*, recommended combined therapy with Aureomycin and streptomycin, and felt that Aureomycin alone was clearly superior to the combination of streptomycin with sulfadiazine and to chloramphenicol.[1998] The Joint FAO/WHO Expert Committee recommended daily doses of 1 to 2 gm. streptomycin or dihydrostreptomycin combined with 2 gm. of Aureomycin or Terramycin for 21 days.[2292]

In 60 patients with brucella infection in the United States, combined therapy with either Aureomycin and streptomycin or Terramycin and streptomycin was followed by a relapse rate of 5%. In 17 cases *B. abortus* was recovered, *B. suis* in 14, *B. melitensis* in 10; the organism was recovered but not identified in two, and was not cultured in 17.[943] In *B. melitensis* infection in Egypt, approximately two thirds of 39 patients treated with Terramycin, streptomycin or chloramphenicol alone relapsed.[1166] In Mexico the relapse rate of infections with *B. melitensis* after treatment with Terramycin alone was 30 to 50% in one series of 84 patients;[1819] two of 11 patients in another study relapsed.[1190] Combined Terramycin-streptomycin therapy of 23 *B. melitensis* infections in Egypt yielded a 14% relapse rate.[1360] A few patients responded to the administration of chloramphenicol[512] and to a combination of streptomycin and sulfadiazine.[827]

Joint involvement in acute brucellosis responded to Terramycin alone[169] and to Aureomycin-streptomycin combination.[575] Spondylitis responded to combinations of Aureomycin or Terramycin with streptomycin,[943, 1169] but one patient with spondylitis was not controlled on Terramycin alone.[1190] Surgery was recommended in addition to drug therapy in patients with chronic circumscribed, fibrotic lesions or a localized abscess.[2217]

In "chronic brucellosis" Aureomycin used alone produced some improvement in about 75% of patients; this was temporary, with return of symptoms usually within a few weeks or months.[844] Results with chloramphenicol were less satisfactory.[845]

Rat Bite Fever

Sodoku. Two children had recurrent fever, skin eruption and symptoms referable to the respiratory, intestinal and central nervous systems. One child died of encephalitis two and one-half years after onset of the illness, while the other recovered following Aureomycin therapy almost four years after the probable date of infection. An organism resembling *Spirillum minus* was recovered repeatedly from the blood of both patients, and was also demonstrated on dark field examination of a skin lesion in the second patient. Both children had a history of possible infection from rats.[1916]

Haverhill Fever. Four children were reported with "Haverhill fever"; in three of them the disease developed two to three days after a rat bite.[538, 684, 2204] The symptoms were "septic" or "relapsing" fever, maculopapular or urticarial lesions, and arthritic swelling of various joints. *Streptobacillus moniliformis* was isolated from the blood of three patients and from a skin pustule in the fourth.[2204] Specific streptobacillary agglutinins reached titers of 1: 160 to 1: 320 in two children.[538] One infant responded promptly to streptomycin therapy,[684] one to penicillin,[2204] and the other two apparently to Aureomycin.[588] In two patients, *Streptobacillus moniliformis* was repeatedly isolated by blood culture on media containing 20 to 30% serum or ascitic fluid during the first eight weeks of their illness, despite daily administration of 2 million units of penicillin. But thereafter only a pleuropneumonia-like variant (the L_1 form of Klieneberger) was recovered.[588]

Mycotic Diseases of the Joints

Coccidioidomycosis. Coccidioidomycosis was frequent in the San Joaquin Valley and nearby areas, and probably in Argentina. The disease resulted from the entrance of spores of the fungus (*Coccidioides immitis*) through the respiratory tract.[569, 1861] The danger of infection to laboratory personnel handling cultures was emphasized.[636, 1861] Exogenous reinfection was unusual.[1861]

Positive skin tests indicated that at least 60% of the primary infections were benign and unrecognized. The symptomatic primary infection was usually a mild influenzal or more severe pneumonia-like disease, often with marked weight loss. Erythema nodosum, conjunctivitis, arthralgia and eosinophilia occurred in about 20% of the symptomatic patients. In the San Joaquin Valley the coccidioidin skin test was positive in 432 of 453 patients with erythema nodosum.[1861]

Progressive, disseminated infection (coccidioidal granuloma) was rare, especially in the white race, where it occurred only once in 500 or more patients. Granulomatous involvement of the lungs often resembled tuberculosis, with nodular lesions, cavitation, pneumonitis with adenopathy, or a final miliary spread.[1861] Liver, kidney, spleen, pancreas, bone and bone marrow were involved.[636, 1861] One of three patients with pericarditis died.[1241] Osseous lesions were not uncommon in the disseminated type. Single or multiple destructive lesions involved the ends of the long bones, with a predilection for bony prominences around the knees and ankles and also for the diaphyses of the bones of the hands or feet. Diaphyseal destruction or marginal erosion with periosteal new bone formation resembled osteomyelitis, and cartilage or synovial involvement was present as in tuberculosis. Multiple swollen joints resulted from epiphyseal involvement, and soft tissue abscesses and draining sinuses were not infrequent.[569, 636, 1861] Bone lesions in one group of 26 children had a relatively good prognosis for eventual recovery.[569]

A positive coccidioidin skin test was diagnostic of primary infection,[569, 1241, 1861]

but this test was negative in 70% of disseminated infections.[1861] Cross reactions were not uncommon with histoplasmin and blastomycin. The precipitin test was positive in severe primary infection. Complement fixation was positive in disseminated disease, and a falling titer was considered a good prognostic sign.[1861] The fungus was demonstrated by microscopic examination of tissue removed at biopsy, by culture, or following inoculation into the testes of guinea pigs; occasionally the organism was found in direct smears.[686, 1241, 1861]

There was no specific treatment. Surgical excision was advised for localized granulomatous lesions.[686, 1861]

Histoplasmosis. Infection with *Histoplasma capsulatum* was relatively common and, with few exceptions, benign. The majority of patients had an unrecognized primary infection which resembled "grippe" or a mild pneumonitis. Some patients had a nonfatal disseminated infection, and a few succumbed with systemic involvement. Skin, serologic tests and cultures were usually positive in the chronic disease, but skin tests were negative in the acute, fulminating type.[1052] Although no evidence was found to suggest transmission from dog to man, the dog was regarded as a potential source of infection because the fungus was found in sputum, saliva, vomitus, feces and urine.[1688] Portmortem examination in a 17 month old infant revealed lesions of the lungs, liver, spleen, lymph nodes and bone.[762] [Bone lesions are infrequent in histoplasmosis.—Ed.]

Blastomycosis. *Blastomyces dermatitidis* was restricted to the North American continent, especially the Midwest, the Ohio River Valley and North Carolina.[1860] Agricultural workers living in unhygienic surroundings were most commonly affected. The fungus gained entrance to the human body through the respiratory tract or through abraded skin; direct man-to-man transmission was not proved.[1434, 1860] The disease usually presented as a pulmonary infection or with cutaneous manifestation.[1434] The lung appeared to be the site of infection in 60 patients, with secondary hematogenous spread to the skin and other organs;[1860] these included the larynx, bones, liver, kidneys, spleen, serous membranes and central nervous system.[1434] Moist cover-slip preparations of exudate or scrapings, stained sections, cultures, complement fixation and skin tests demonstrated infection with the fungus.[604]

Blastomycotic osteomyelitis was observed in many locations.[33, 2121] Vertebral involvement resembled tuberculosis, with narrowing of the disc spaces, destruction of bone with collapse of vertebral bodies and spread from segment to segment under the anterior spinal ligament.[131] Treatment with stilbamidine intravenously, plus Propamidine locally, apparently cured three patients with systemic involvement.[1852, 1853] Massive doses of Aureomycin administered with potassium iodide were beneficial in two patients with systemic disease.[1434] In one case with multiple bone involvement and draining sinuses, recovery with bone regeneration followed treatment with potassium iodide.[2121] Amputation was necessary in two patients with bone involvement.[33]

Actinomycosis. Involvement of the mandible, ribs, humerus, ilium, phalanges, spine and liver was reported.[33, 131, 266, 426, 1435] Diagnosis was made by direct examination of purulent material from abscesses or sinuses, or by culture under anerobic conditions.[426, 1435]

A total of 65 reported cases of actinomycosis of the spine were reviewed.[426] Although some differentiated between the radiologic appearance of primary and secondary vertebral involvement,[131] others believed that actinomycosis of the vertebrae was always secondary to contiguous infection.[426] The disease usually involved several vertebrae, affecting the bodies, pedicles, transverse processes and heads of neighboring ribs, but sparing the discs. Dense bone sclerosis extending into the bodies and surrounding many small abscess cavities produced the "honeycomb," "lattice" or "soap bubble" appearance; long bony spurs bridging the vertebrae were also reported.[131, 266, 426]

Penicillin in doses of up to 1 million units daily, in combination with a sulfona-

mide administered for as long as a year or two, was believed to arrest the disease.[33, 266, 426] Four patients were apparently cured after use of Aureomycin.[1435] Resection of infected bone was recommended.[33, 131]

Rarer Forms of Specific Infectious Arthritis

Several unusual types of acute infectious arthritis were reported. A premature infant with *Pseudomonas aeruginosa* infection of the knee responded to dihydrostreptomycin therapy.[401] Two infants with meningitis and pyarthrosis due to *H. influenzae* recovered with some residual joint disability.[1094, 1947] Pyarthrosis with subcutaneous emphysema of both knees occurred in a patient who died of a generalized infection with *Escherichia coli* and a nonhemolytic streptococcus.[1473] A "lepra" reaction, with hot swollen joints, fever, and a skin eruption which subsided on the fifth day, was seen in a patient with lepropsy.[1472] Twenty-one cases of pyogenic arthritis and osteomyelitis following the 1951 smallpox epidemic in Calcutta were reported.[102] [There is nothing in the clinical description, x-ray findings or response to penicillin in these cases to distinguish them from the usual forms of these diseases, except their occurrence coincident with or within two to six weeks after desquamation from variola.—Ed.] Salmonella were recovered by culture from the blood and from material aspirated from the joint of a patient with unilateral sacro-iliac arthritis.[1390] An acid-fast organism, proved not to be *Mycobacterium tuberculosis* by culture and animal inoculation, was recovered from the knee of a patient with low grade mono-articular arthritis.[1492] *Leptospira pomona* produced an acute arthritis and myocarditis closely simulating acute rheumatic fever.[2073]

Acute transient synovitis of the hip joint occurred in 13 children under 10 years of age, and was believed to be a hypersensitivity reaction of the synovial membrane to a focus of infection. This lesion subsided, usually in one to three days, and had to be distinguished from osteomyelitis, septic arthritis, acute epiphysitis, tuberculosis, and Legg-Perthes' disease.[589]

The Adrenal Cortex and Rheumatic Diseases

As further efforts were made to define the mode of action of corticotropin and adrenocorticosteroids in the rheumatic diseases, knowledge of endocrine physiology continued to expand rapidly. These advances were the subject of several excellent reviews.[425, 610, 676, 1044, 2001] [This section deals with contributions having a direct bearing on aspects which the rheumatic diseases have in common. Additional work bearing on the individual diseases will be found in appropriate sections.—Ed.]

Pituitary-Adrenal Physiology. Further studies emphasized the remarkable rapidity with which the pituitary-adrenal mechanism responds to stimulation. The rapidity of response of the anterior pituitary of rats to intravenous histamine was of the order of 10 seconds or less.[825] The rapid disappearance of ACTH from the blood was confirmed. The "half-life" of exogenous ACTH in experimental animals was found to be about five minutes,[1748] and that of endogenous ACTH about one minute.[2086] A significant concentration of corticotropin was found in the kidneys five to 15 minutes after its injection, although none could be detected in the urine.[848] In humans, no significant ACTH effect could be detected by a sensitive method in the blood of normal, non-stressed men, although detectable amounts were found in the blood of patients with Addison's disease and in patients who had received cortisone.[2087] When an ACTH preparation labeled with I^{131} was injected into rats, radioactivity appeared promptly in the adrenals, and disappeared rapidly.[1986] An increase in the plasma level

of 17-hydroxycorticosteroids in children was found to be most consistent at two hours following the intramuscular injection of ACTH, with a rapid drop in four to six hours.[1707] [Data on intervals of less than two hours were not reported.—Ed.] The rapid rise and fall of these plasma levels in conjunction with continuous intravenous infusions of corticotropin indicated that "the pituitary and adrenal hormones are both rapidly released and rapidly disposed of."[1537]

The ability of relatively small quantities of ACTH to produce sustained adrenocortical stimulation when administered by continuous intravenous drip to human subjects was first noted by Gordon[805] and promptly confirmed.[1076, 1363, 1696, 1737] Systematic studies established that the magnitude of adrenal stimulation by the continuous intravenous route depended on duration of administration rather than the amount of ACTH administered, and that maximal stimulation in an eight-hour period of administration was obtained with a dose of 20 mg.[1738] At about the same time, certain (somewhat impure) preparations of ACTH were shown to be inactivated at the site of injection when given by the intramuscular route. Subjects resistant to intramuscular injection of such preparations of ACTH responded normally to intravenous administration of the same material.[748, 1738] These facts were utilized in the development and testing of preparations of corticotropin with prolonged action when given by the intramuscular route.[286, 656, 1230, 2279]

The multiple factors regulating the secretory activity of the anterior pituitary and adrenal cortices were reviewed.[1044, 1841] Further studies emphasized the sharp limitations of the use of ephedrine,[263] epinephrine,[205, 563, 977, 1123] and insulin-induced hypoglycemia[1637] as means of stimulating the pituitary-adrenal mechanism. While eosinopenia was often produced, other evidences of adrenal cortical stimulation were not obtained. Further studies indicated that, while some of the metabolic changes accompanying artificial fever can be explained on the basis of hormonal stimulation, other effects cannot.[1177] [The results of subsequent work suggest that the response of "stress" is mediated through other mechanisms as well as through the pituitary-adrenal axis.—Ed.]

Technical advances in methods for study of adrenocortical function were rapid. Reasonably specific methods for determining the 17-hydroxycorticosteroids in the urine[332, 1677a] and in the plasma[1536] provided a direct measurement of cortisone-like steroids and tended to replace determination of 17-ketosteroid excretion and measurement of metabolic effects in investigative studies. The advantage of measuring "corticoids" rather than 17-ketosteroids was noted particularly in children.[2002] Determination of the levels of 17-hydroxycorticosteroids (principally hydrocortisone) in the plasma of 120 normal adults revealed rather wide variation, with a skewed distribution tapering at higher levels, and a surprisingly large day-to-day variation in the same individual. The wide range of plasma 17-hydroxycorticosteroid values suggested a less sensitive homeostatic mechanism that had previously been assumed.[206] Diurnal variation was noted, with maximal levels in early morning, a drop during the day, and lowest levels usually in the evening; a corresponding diurnal variation had previously been noted in the eosinophil counts.[2085] In 26 normal children the plasma levels also ranged widely; values in 27 children with a variety of illnesses did not differ significantly from those of healthy children, both high and low levels being encountered.[608] When corticotropin or oral cortisone was administered, the increases in plasma levels of 17-hydroxycorticosteroids in

normal children did not differ significantly from those in children with various diseases, including acute rheumatic fever.[1707]

Factors influencing the level of eosinophils in the blood were further studied.[226, 326, 1128, 1805, 2085] The eosinopenia following corticotropin was usually, but not always, correlated with an increase in plasma 17-hydroxycorticosteroids. While the eosinophils usually were decreased after epinephrine injections, there was no consistent pattern of response of the 17-hydroxycorticoid level in the plasma. These findings were interpreted as indicating that the eosinopenic response to epinephrine was not mediated through release of these corticosteroids from the adrenal, and that such response to ACTH need not be so mediated.[1123, 1707]

It was demonstrated that cortisone can be converted to hydrocortisone by liver homogenates,[35, 659] and that interconversion from one to the other occurs in vivo in human subjects.[310] While in experimental animals cortisone was much more effective when given subcutaneously as compared with the oral or intrasplenic route,[499] the approximate equivalence of oral to intramuscular cortisone in humans was carefully documented, with respect to both clinical and metabolic effects. With oral administration the effects appeared more rapidly, and were also dissipated more rapidly when the steroid was discontinued.[615, 2128] By intramuscular administration, hydrocortisone acetate appeared less active than cortisone acetate.[1634] [This apparently is due to much slower absorption of hydrocortisone acetate from the muscle.—Ed.]

Rheumatic Diseases as "Diseases of Adaptation." This concept, discussed at length in the Tenth Rheumatism Review, was re-affirmed by Selye.[1872a] "There is no reason to doubt that the organism responds with a stereotyped reaction pattern during stress situations. . . . We also conclude that derangement of this reaction may result in diseases in which maladaptation (and particularly inadequate pituitary and/or corticoid hormone production) represents the major pathogenetic factor." New evidence supporting this concept was derived largely from experimental observations of the effects of growth hormone, or "somatotrophic" (STH) hormone, which has become available in relatively pure form. This hormone—in rats "sensitized by unilateral nephrectomy and a high sodium intake"—shared with desoxycorticosterone acetate (DCA) the ability to produce rheumatic-like myocarditis, periarteritis and malignant nephrosclerosis, and the effect of the two hormones administered simultaneously greatly increased these effects.[1872] Such experimental equivalents of "collagen disease" were produced only in the presence of functioning adrenal tissue.[1871] Antagonism between STH and cortisone was demonstrated with respect to anatomic changes and to antiphlogistic effect as judged by a "topical irritation arthritis";[1874] the increased susceptibility to infection of animals receiving ACTH or cortisone was prevented by suitable doses of STH.[1873]

Attempts to reproduce the experimental observations on which Selye's theory rests were not uniformly successful. Others found that DCA did not induce pathologic changes with a high degree of reproducibility from one experiment to the next, although when changes occurred they were uniformly present throughout the DCA-treated animals of any given experiment. Inhibition of the DCA-induced pathologic changes occurred only when large doses of ACTH or cortisone were given, and not with doses considered to be in the physiologic range.[1801] Harrison presented evidence indicating that selective damage to the

zona fasciculata of the rat adrenal was a prerequisite for the production of arthritis by DCA administration; such selective damage could be produced by inadvertent interference with the blood supply during unilateral nephrectomy, as well as by other means.[900, 901, 902] Studies of the ability of ACTH and cortisone to suppress "formalin-arthritis" yielded conflicting results. [These studies are summarized in the section on experimental arthritis.—Ed.]

Arthritis was produced in rats given purified growth hormone daily for six months. Joint tenderness and swelling were noted, and x-rays showed "irregularity and erosion of condylar margins, localized osteoporotic areas at condyles . . . and lipping and calcification at joint margins." Such changes occurred in all of five surviving adrenalectomized and ovariectomized animals, but in only one of 10 intact animals.[1734]. [It is of interest that the changes observed were as compatible with osteoarthritis as with rheumatoid arthritis. Further characterization of the arthritis produced by purified growth hormone, including detailed histologic studies, is needed.—Ed.]

After careful evaluation of their own experimental results and those of others, Rosenberg, Woodbury and Sayers concluded: "Neither the experiments recorded here nor other evidences in the literature support the concept that stress, through the mediation of the adrenal cortex, is an etiologic agent in the mesenchymal tissue diseases. Nor is there evidence to support the notion that hypoactivity of the adrenal cortex is involved in the development of mesenchymal tissue diseases." [1801] Bauer pointed out that "the combination of conditions of rat experiments upon which this etiologic concept is based is rarely, if ever, encountered in humans." [121] [Recent advances resulting from the identification and isolation of the physiologic "mineralocorticoid," aldosterone, do not lend weight to Selye's hypothesis. Primary aldosteronism due to adrenal cortical tumor was clearly defined as a clinical entity by Conn in 1954. Its clinical and pathologic manifestations include renal damage and hypertension, but no other manifestation of any rheumatic disease.—Ed.]

Mode of Action of Adrenal Corticosteroids in the Rheumatic Diseases. "It is an undoubted fact that experience in the use of ACTH and cortisone in the clinical fields has far outrun the advance in knowledge of their mode of action in the rheumatic diseases" (Duthie [566]). Most authors agreed that their action in these diseases was in no way specific, and appeared to depend upon a suppression of the inflammatory process, or a protection of the cell from a variety of injurious agents.[566, 676, 1170, 1412, 1801] The possibility of an increased requirement of inflamed tissues for corticosteroids was not supported by direct measurement of blood 17-hydroxycorticosteroid levels; the arteriovenous differences in such levels showed no consistent drop, even across areas of marked inflammation.[1537]

Effect on Ground Substance. The ability of corticosteroids or ACTH stimulation to inhibit the spreading action of hyaluronidase in experimental animals was confirmed by some observers [69, 194, 333, 980, 1585] but not by others.[922, 1445] Alterations in the spreading reaction resulted with estrogens [921] and chorionic gonadotropin,[1585] but not with corticosterone or testosterone.[921] Prolonged systemic or local treatment resulted in a paradoxic enhancement of hyaluronidase spread, interpreted as indicating an alteration in the physical state or amount of ground substance, specifically related to steroids of adrenocortical origin.[921, 922, 923] Such change in the characteristics of the ground substance was also suggested by increased resistance to intracutaneous injection of the skin following cortisone administration,[2270] and by histochemical

changes observed in the region of hydrocortisone acetate crystals persisting after their injection into human skin.[790] Others felt that the steroids truly inhibited hyaluronidase activity, perhaps by inducing a deficiency of sulfhydryl-containing enzymes.[40] No effect on the spreading reaction was found in patients treated with cortisone.[980]

Further studies suggested that the nonspecific hyaluronidase inhibitor in sera of experimental animals was increased by pituitary-adrenocortical stimulation.[799] Additional work on the influence of hormones on the rapidity of recovery in the urine of phenolsulfonphthalein injected into the joint led to questioning of the validity of this method for measurement of the permeability of the synovial membrane.[957, 1618]

Effect on Hypersensitivity Phenomena. Many reports appeared concerning both clinical and experimental studies of hypersensitivity as influenced by adrenocorticosteroids. It is possible to review only those studies which deal with hypersensitivity-induced analogues of the rheumatic diseases; such studies do, however, reflect the general trend of decreasing emphasis on antibody production or antigen-antibody combination as the point of action of these hormones. Bennett, Berthrong and Rich added to their observations on the ability of ACTH and cortisone to suppress the experimental cardiovascular lesions produced by anaphylactic hypersensitivity: only 14 of 59 rabbits receiving one of these hormones developed lesions, compared to an incidence of 51 in 59 control animals.[156] The results of others were uniformly of the same order.[454, 810, 1422, 1488] While in earlier studies Germuth and co-workers found evidence to support the view that cortisone and ACTH acted to inhibit antibody formation,[744, 745] in subsequent work with serum-sickness type of hypersensitivity they found these hormones to suppress the incidence of cardiovascular lesions without any effect on the rate of elimination of antigen or appearance of antibodies.[743] The conclusion that corticosteroids in some way protected against the damaging effects of antigen-antibody union was supported by the demonstration of protection against lesions produced by passive sensitization, where the effect could not be attributed to suppression of antibody production.[892, 2157]

Particularly impressive were the observations of Ebert and Wissler, who used the rabbit ear chamber technic to study the in vivo manifestation of this form of serum disease. They found that cortisone treatment effected a profound reduction in the degree of vascular damage, with better maintenance of vascular tone, a more normal appearance of vascular endothelium and reduction in the sticking of leukocytes to the endothelium. As a result there was a decrease in diapedesis of leukocytes and reduction in the accumulation of exudate. They concluded that "cortisone produces a profound effect on the integrity and reactivity of the small blood vessels and the suppression of the in vivo manifestations of serum disease is due to this nonspecific effect rather than to suppression of antibody formation or antibody-antigen union."[576] Other avenues of investigation also suggested that the hormonal control of inflammatory reactions may be exerted through action on the small blood vessels and capillaries.[1445, 1446, 2157]

After reviewing the information available as to the role of adrenal steroids in infection and immunity, Kass and Finland stated: "Most of the evidence suggests that ACTH and cortisone have little effect on antibody formation. . . . It is more likely that [they act] to alter the capacities of the host's tissue to respond to certain types of irritants, irrespective of the involvement of immune mechanisms."[1108]

Effect on Granulation Tissue and Inflammation. Delay in the healing of experimental wounds by the action of corticosteroids was amply confirmed in further studies; the differences between species of experimental animals and other factors influencing the results were more adequately defined.[31, 103, 126, 128, 369, 396] Cortisone added to tissue cultures was reported to have no effect on fibroblasts,[32, 99, 741, 2015] although in one carefully documented study, both cortisone and hydrocortisone as

free alcohols definitely inhibited the migration of fibroblasts in tissue culture.[1111] [The discrepancies are undoubtedly due to differences in procedures; the solubility of the steroid may be of particular importance.—Ed.] It was shown that the oxygen uptake of slices of granulation tissue from cortisone-treated animals was one third that of granulation tissue from untreated animals.[1842]

Cortisone was also demonstrated to inhibit inflammatory reactions produced experimentally by a variety of methods.[851, 1459, 1487, 1592, 2323] While one observer felt that the primary effect was an inhibition of angioblastic and fibroblastic proliferation,[2323] others noted suppression of the earliest inflammatory changes, such as vascular margination of leukocytes, diapedesis, capillary hemorrhages and edema.[1459, 1487] The eye offered an unusually good site for such studies, and it was possible to demonstrate that some of these effects were not exerted by influencing the vascular component of the inflammatory process.[104, 562, 2286] There was considerable evidence that the action of cortisone in suppressing inflammation was exerted at the local tissue level.[789, 1447, 1886, 2287] [The ability of intra-articular injection of hydrocortisone to suppress the clinical and joint fluid abnormalities in rheumatoid arthritis is regarded as additional evidence of the anti-inflammatory action of these steroids at the tissue level.—Ed.]

Several explanations were offered for the way in which this anti-inflammatory effect is mediated [although none of them is supported by very convincing experimental evidence.—Ed.]. These included inhibition of tissue utilization of sulfhydryl enzymes essential for tissue regeneration,[1877] blocking of the effects of exudative products on capillary fragility,[1445, 1446, 1447] and inactivation of fibrinolysin in the tissues, mediated through humoral substances released from the spleen.[2154, 2155] [The last is difficult to reconcile with evidences of suppression of inflammation at the local tissue level.—Ed.] Although direct studies indicated that ACTH and cortisone did not alter the reparative process in scorbutic animals,[423, 2158, 2277] Teilum concluded that the mechanism by which cortisone influenced mesenchymal tissue was an indirect one, mediated by ascorbic acid.[2114] Cortisone was shown to inhibit the synthesis of chrondroitin sulfate in embryonic chick muscle in tissue culture and in healing wounds in experimental animals, as demonstrated by fixation of labeled sulfate. Concentrations which affected sulfate fixation had no apparent effect on initial migration of fibroblasts.[1253]

Biochemical and Physiologic Effects. The well recognized metabolic effects of these hormones have served to explain the untoward effects observed during their administration, but have thrown little light on the mediation of their suppressive action.[2001] Attempts to explain their action on a common biochemical basis were relatively fruitless. The indirect evidence was summarized, suggesting "that the clinical effect of ACTH and cortisone in the rheumatoid syndrome is mediated by retardation, through sulfhydryl deprivation, of essential enzyme systems that depend on the presence of sulfhydryl for their integrity."[39] However, direct experimental studies failed to show changes in the sulfhydryl content of tissues in animals given ACTH,[2164] and studies of the blood glutathione levels in patients receiving ACTH or cortisone yielded inconclusive results.[949, 1008a] Lovgren found that increases in blood pyruvic acid were associated with clinical improvement.[1325] No changes were found in the urinary excretion of hexosamine or glucuronic acid during treatment with corticotropin.[75]

Borden and co-workers demonstrated changes in the levels of certain amino acids in urine and plasma during administration of ACTH to patients with rheumatoid arthritis. Since these changes differed from the response of normal subjects receiving ACTH, the observations were cited as additional evidence of a correlation between amino acid metabolism and the "remission factor in rheumatoid arthritis."[235] Of particular interest were the changes in histidine excretion, without significant alteration of the plasma level, since this amino acid had previously been found to be excreted in large amounts in remissions associated with pregnancy and jaundice. Grob confirmed the increased excretion of histidine during ACTH and cortisone ad-

ministration, but presented evidence that this effect was primarily renal in origin and chiefly attributable to a decrease in tubular resorption.[846] In mice, corticotropin increased the rate of incorporation of labeled histidine into body protein.[1558] Corticosterone (compound B) produced no discernible clinical improvement in rheumatoid arthritis,[365, 1777] although its administration reproduced most of the known metabolic effects of cortisone and hydrocortisone.[415]

In extending previous studies, Robson and Duthie found a significant elevation of capillary resistance "invariably associated" with clinical responses to ACTH and cortisone in a variety of diseases, and felt that this effect might provide a clue as to the mode of action of these hormones.[1780] Alleviation of pain during induced hyperadrenalism was attributed to control of inflammation, as no direct analgesic effect could be demonstrated.[2160]

Untoward Effects. Much attention was devoted to the undesirable effects which develop during treatment with corticotropin or corticosteroids.[98, 687] The frequency of such undesirable effects varied in different series from 23%[1381] to 65%;[2115] and they were seen to some extent in 83% of 36 essentially normal young men treated with substantial amounts of ACTH or cortisone for 31 consecutive days.[56] Determining factors appeared to be dosage, duration of treatment, individual susceptibility, and nature of the disease treated.[1381, 2001, 2115]

The potential hazards of long-term therapy with ACTH and cortisone were emphasized by a study of the natural history of Cushing's syndrome. The clinical course of 212 patients with spontaneous hyperadrenalism was characterized by a high incidence of mental abnormalities, poor wound healing or unusual intercurrent infections. In 114 autopsied cases, the major causes of death were infection, cardiovascular disease and neoplastic disease. An extremely high incidence of arteriosclerosis and osteoporosis was noted.[1668] [These observations represent the course of uncontrolled hyperadrenalism. In the therapeutic use of these hormones, the physician is able to control both the magnitude and the duration of the induced hyperadrenalism. The need to exercise this control is obvious.—Ed.]

Many of the untoward effects were attributable to the physiologic results of hyperadrenalism.[2001] These included the well recognized somatic changes of Cushing's syndrome, such as obesity, moon face, buffalo hump, supraclavicular fat pads, hirsutism and acne.[189, 222, 223, 367, 493, 699, 751, 979, 1273, 1363, 1370, 1381, 1554, 1684, 1695, 1706, 1802, 1803, 2030, 2032, 2033, 2115, 2235] Sodium retention accounted for fluid retention[223, 367, 493, 699, 1273, 1363, 1381, 1684, 2030, 2032, 2033, 2115, 2282] and presumably for cardiac enlargement[2235] and congestive cardiac failure.[699, 1706, 2030, 2032, 2033] Hypokalemia was observed,[367, 493, 699, 751, 1514, 1706] and at times lowered plasma potassium levels which were not associated with electrocardiographic changes.[1307] Hypertension occasionally developed,[367, 493, 699, 1273, 1363, 1370, 1554, 1684, 1802, 2030, 2032, 2115] but was stated to occur rarely in patients without renal disease, whereas a rise in blood pressure was the rule in patients with renal damage of varying types.[1633]

Diabetes. While evidence of impaired glucose tolerance, hyperglycemia or glycosuria occurred during hormone administration, the development of permanent diabetes was rare.[189, 199, 221, 223, 303, 367, 699, 751, 1008a, 1273, 1370, 1802, 2030, 2264] In one series of over 500 patients, less than 1% developed true diabetes mellitus, and in each instance there was a "predisposition" to the disease.[230] [Since glucose tolerance tests were not done prior to hormone administration, these may be examples of aggravation of preëxisting but mild diabetes mellitus.—Ed.]

Osteoporosis. The frequency of osteoporosis, often with spontaneous fracture, cannot be estimated from several case reports.[189, 223, 367, 704, 2030, 2033, 2113, 2235] It occurred in three of 66 patients receiving ACTH or cortisone for a variety of diseases, nearly all treated for six months or less.[2115] In another series of 56 patients, 7.1% developed osteoporosis.[1370] Women and older patients were more likely to develop this complication; predisposing factors were bed-rest, disease activity and the postmenopausal state. Most, but not all, patients developing osteoporosis were on relatively large doses (over 500 mg. of cortisone per week) for long periods of time (eight to 26 months).[221, 503] [Osteoporosis may be a regularly occurring feature of the underlying disease being treated. Thus, the groundwork for compression fractures may be present before the treatment is started. It is well established that steroid therapy induces a negative nitrogen balance. The extent to which the complications of osteoporosis are accelerated by these hormonal agents cannot be fully evaluated at the present time.—Ed.]

Skin Changes. Acne was attributed to the androgenic effects of adrenocortical steroids, and occasionally was very severe.[292] Pigmentation of the skin was at times marked.[189, 223, 292, 493, 751, 1370, 1802, 2030, 2033] [While this simulates the pigmentation of Addison's disease, and indeed is probably due to the same mechanism, its development is not evidence that ACTH or cortisone has induced adrenal insufficiency.[1419]—Ed.] The occurrence of cutaneous arterial spiders following the use of ACTH was well documented.[1981] Purpura was also reported.[223, 367, 699, 2032] In some cases this appeared to be due to ascorbic acid deficiency.[997, 2016] [Usually there is no evidence of a scorbutic factor in the purpura which develops during hormone therapy.—Ed.]

Psychologic and Central Nervous System Disturbances. Psychic disturbances, ranging from exaggerated degrees of the usual euphoria to severe psychoses of various types, occurred with sufficient frequency to constitute a real hazard in therapy.[189, 223, 236, 363, 364, 657, 662, 681, 699, 751, 764, 979, 995, 1273, 1370, 1381, 1533, 1554, 1684, 1695, 1706, 1728, 1769, 1802, 2033, 2115, 2134] In several series of patients the frequency of distinctly aberrant psychologic reactions was 5.5% of 128 patients,[2032] 6.3% of 63 patients,[1684] and 15% of 66[2115] and of 80[800] patients, respectively. Most of the psychoses were mild, transient and self-limited when the hormones were withdrawn, but some required shock therapy, and suicides were reported.[236] Most observers felt that the occurrence of severe psychic disturbance was unpredictable, and that it was not related to size or duration of dosage or to biochemical changes.[367, 800] The occurrence and nature of psychoses in spontaneously occurring Cushing's syndrome indicated that these reactions could be attributed to hyperadrenalism.[764, 2139]

The psychologic and emotional responses of patients receiving ACTH or cortisone for a variety of diseases were studied intensively and the results expressed in psychodynamic terms.[1288, 1425, 1728, 1787, 1788] In addition to the pharmacologic effect, it was apparent that the responses were related to the psychologic significance of the patient's illness and the symbolic value of an alteration in symptoms, as well as to the nature of the patient's fantasies about the action of the substance administered.[1425, 1787] Electro-encephalographic changes were demonstrated during administration of ACTH and cortisone, but such changes were not correlated in incidence or degree with the occurrence of psychosis.[765, 1288, 1655, 2212] Corticotropin had no significant effect on cerebral blood flow and oxygen consumption in patients with various diseases.[27]

Another serious complication was the development of convulsions, with or without accompanying psychosis.[225, 543, 740, 1201, 1381, 2038] In two fatal cases, autopsy revealed no pathologic changes sufficient to account for the convulsions and coma.[225, 740] [It should be remembered that convulsions are not uncommon in natural course of systemic lupus erythematosus. However, several of these cases were in patients believed to have rheumatic fever and rheumatoid arthritis, in which convulsions are most uncommon.—Ed.] Other symptoms reported included headache,[1370, 1381, 1554] vertigo and blurring of vision.[1706]

Peptic Ulcer. There were numerous reports of activation of gastric or duodenal ulcers during cortisone or corticotropin therapy.[189, 311, 704, 824, 959, 1143, 1162, 1179, 1273, 1335a, 1381, 1483, 1695, 1703, 1706, 1830, 1965, 2032] In some cases there was no previous ulcer history.[311, 824, 1703] The ulceration was often first manifested as a complication, such as perforation[824, 1016, 1143, 1162, 1179, 1335a, 1830, 1831, 1965, 2030, 2033] or hemorrhage.[311, 491, 699, 704, 959, 1381, 1830, 2234, 2235] Of 18 cases reviewed from the literature, 12 manifested perforation, hemorrhage, or both; there were five deaths from complications of peptic ulcer.[1162] Gastrointestinal bleeding also occurred in the absence of lesions demonstrable by x-ray.[704, 1684]

The incidence of peptic ulcer in patients receiving these hormones varied: there was one case in each of a series of 44 patients,[704] 130 patients[1381] and 128 patients;[2032] but three ulcers were reactivated in another group of 79 patients.[1965] Not all patients known to have ulcers became worse during cortisone or corticotropin administration.[704, 824, 1839] A consistent increase in the basal and nocturnal gastric secretion of acid and pepsin, and in urinary uropepsin excretion, was demonstrated in normal subjects and in patients receiving large doses of ACTH.[824] However, the administration of ACTH or cortisone did not increase the incidence of ulcers in dogs after the Mann-Williamson procedure.[1835]

Intercurrent Infection. Hyperadrenalism was believed to enhance a variety of bacterial infections by delaying and inhibiting the initial inflammatory response and the formation of granulation tissue, and by virtue of its ability to break down protective mechanisms of natural resistance as well as to suppress the clinical signs of inflammation.[1458] [These effects are adequately supported by extensive experimental studies of infections in animals, the details of which are beyond the scope of this review. They were comprehensively reviewed by Kass and Finland.[1108] The clinical problems arising from infections during the use of corticotropin or adrenocortical steroids are related chiefly to their effect in causing the infection to spread and in causing the infection to be unrecognized.—Ed.]

Activation or spread of tuberculosis was of special concern. The development of tuberculous meningitis[537] and of miliary tuberculosis[271, 481, 897, 1026, 1184, 2179, 2231] during or closely following the use of corticotropin or cortisone was recorded. [It is noteworthy that most of these were in patients under treatment for systemic lupus erythematosus.—Ed.] The activation of pulmonary tuberculosis in patients receiving these hormones for rheumatoid arthritis was described repeatedly.[689, 1167, 1632, 1675, 1706, 2138] Other infections included pneumonia,[367, 1381, 1458, 1706] purulent pericarditis,[1458] peritonitis,[1458, 1706, 1823] and abscesses at the site of intramuscular injection.[1010, 2115]

Impaired Wound Healing. While instances of delayed wound healing[127, 367, 1273, 2115] and even rupture of the abdominal wall[1250, 2235] were reported in patients receiving corticotropin or cortisone, in most patients receiving these agents the healing of surgical wounds was normal.[127, 672, 699, 1706, 1772, 2030]

Thrombophlebitis and Thrombo-embolism. Cosgriff analyzed 40 instances of thrombotic and embolic accidents which occurred in 28 patients out of an estimated 700 patients receiving corticotropin or cortisone. Ten of these patients had one or more episodes of pulmonary embolism. In 18 instances the thrombotic complication developed during hormone administration, and in 22 after the discontinuation of therapy. Venous thrombosis was more frequently inflammatory in nature, rather than a bland phlebothrombosis.[436] Others observed thrombophlebitis [271, 367, 704, 1703, 1706, 2030, 2032, 2033] and pulmonary infarction.[1706] While some patients with thrombo-embolic episodes showed considerable shortening of their venous clotting time, especially with methods using heparin as a retarding agent,[437] other workers were unble to detect a significant alteration in coagulation of whole blood following the administration of ACTH and cortisone.[634] Patients receiving cortisone were found to be hyporeactors to a heparin tolerance test.[346] [There is need for more information as to the effect of adrenocortical steroids on blood coagulability. While the possibility cannot be ruled out that the thrombo-embolic complications may be more closely related to the underlying diseases than to the hormonal agents employed, the frequency of such complication does seem greater than might be expected.—Ed.]

Hyperlipemia. While ACTH and cortisone administration was associated with changes in the serum lipid partition in man,[11, 1228] hyperlipemia presented a problem in therapy only in a case of dermatomyositis.[2264] Examination of the aortas of 33 patients under the age of 21 years who had received the hormones before death revealed an apparent increase in the deposition of lipid in the intima and media of the younger subjects.[628] Administration of cortisone to rabbits produced a marked lipemia.[1744]

Other Effects. Manifestations which may be due to effects on other endocrine glands included altered libido [1273, 2033] and menstrual irregularities.[367, 699, 1370, 1554, 1706, 2033] Conception occurred during administration of 100 mg. of cortisone daily, with no untoward effects on mother or child.[1214] Thyroid enlargement,[223] hyperthyroidism [1684] and thyroiditis [2135] were reported. Other conditions developing during ACTH and cortisone administration included coronary insufficiency,[657, 699, 1016, 1184, 1381, 2030, 2032, 2033] cerebral vascular accidents,[953, 1706, 2030, 2032, 2033] peripheral vascular occlusion,[699, 2030, 2033] aplastic anemia,[1966] granulocytopenia,[2044a] generalized vasculitis,[1273, 2235] and peripheral neuropathies.[1706, 2033] [Some of these may well have been coincidental or associated with the natural course of the disease under treatment, rather than attributable to the hormone administration.—Ed.]

Well defined hypersensitivity to corticotropin was described, with anaphylactic type of reaction to both intramuscular and intravenous administration.[553, 642, 2070, 2261] [Such reactions are more likely to be manifest in patients with adrenal unresponsiveness—such as Addison's disease or cortisone-induced adrenal atrophy.—Ed.] Development of neutralizing antibodies to ACTH was suggested by loss of clinical responsiveness to the drug.[807] But in one case in which such an antibody was demonstrated, further studies established that the antibody had no antihormone properties and was probably produced in response to the injection of a pituitary impurity.[368]

Adrenal and Pituitary Suppression. Suppression of endogenous adrenocortical activity resulting from the administration of corticosteroids was reflected in anatomic evidences of adrenocortical atrophy [159, 1570] and physiologically by impaired responsiveness to corticotropin or to stress.[223, 614, 1831] The changes in the adrenal cortices of patients receiving cortisone prior to death were comparable to those seen in persons in whom the pituitary gland had been destroyed, suggesting that the adrenal atrophy was induced by suppression of secretion of

pituitary corticotropin.[1570] In a study of the adrenal glands of 190 such patients, definite evidence of adrenal atrophy was found in those cases which had received cortisone for more than five days in a total of more than 450 mg. There was evidence of individual variation in susceptibility to this effect of cortisone, and also in the rate at which these reversible changes returned to their original normal state after cortisone was discontinued.[159]

Such adrenocortical suppression was recognized as responsible for postoperative death from irreversible shock following arthroplasty,[1284] following gastrectomy for bleeding ulcer, and following bunionectomy.[1830] Although in one case no steroid had been administered for four and one-half months, adrenal atrophy had persisted.[1830] Salassa, Keating and Sprague felt that it was impossible to predict the severity and duration of adrenal atrophy in patients receiving cortisone, and advised preparation before operation for any patient who had received significant doses of corticosteroids during the preceding three to six months, or who had manifested severe hyperadrenalism during the preceding 12 to 18 months. They proposed intramuscular doses of 200 mg. of cortisone 48, 24 and two hours before surgery, careful observation and prompt use of intravenous cortisone or hydrocortisone during operation and in the first 24 hours thereafter, with gradual tapering of the hormone dosage in the postoperative period.[1831] [While the stress of surgery furnished the most dramatic and tragic examples of the suppression of adrenocortical function, it is obvious that the same dangers are faced by such patients subjected to trauma or febrile illness. There is at least presumptive evidence that the hazards of adrenal insufficiency apply equally to patients who are receiving hydrocortisone, prednisone and prednisolone.—Ed.]

Engleman and co-workers were able to restore adrenal responsiveness by the use of intravenous ACTH and intramuscular ACTH-gel in all of 19 patients who had been receiving cortisone in continuous, uninterrupted administration for 12 to 26 months. But seven of them required administration of corticotropin for four to six days before response occurred, as measured by eosinopenia and increased excretion of urinary steroids.[614] Cytologic changes in the anterior pituitary following cortisone administration[159, 1239] indicated that dysfunction was probably not restricted to the adrenals. Similar changes in the anterior pituitary[159, 1239] and in cells of the hypothalamic nuclei in experimental animals[335] were induced by corticotropin. Such observations led Salassa, Keating and Sprague to caution that it may not be safe to assume that a patient who has normal responses to tests of adrenal cortical function (including a normal response to corticotropin) possesses a normal reserve of adrenal cortical function.[1831]

Mitigation of Undesirable Effects. The best protection against the development of significant undesirable effects continued to lie in the use of the smallest effective daily and total dose (Tenth Rheumatism Review), and careful and frequent supervision of the patient.[1703] The use of a low sodium diet and potassium supplements was widely recommended to avoid complications due to electrolyte imbalance. One group, favoring use of large doses of corticotropin or cortisone, believed that the hyperadrenal manifestations could be modified by dietary manipulation, and recommended a high protein, high fat, low carbohydrate, low sodium, high potassium diet.[1173, 1174] Later they also advised the use of testosterone and estrogen "to decrease induced breakdown of soft tissue and bone."[1171, 1172] Others found that large potassium supplements modified the effects of ACTH on sodium metabolism, but did not alter the effects on protein or carbohydrate metabolism.[158] In animal experi-

ments, testosterone propionate and methyl androstenediol prevented the adrenal cortical atrophy induced by cortisone but did not antagonize the ability of cortisone to suppress inflammation.[2271] [There is no established evidence that dietary manipulation or hormonal supplementation can eliminate the undesirable metabolic effects induced by the hyperadrenal state.—Ed.]

Rheumatic Fever

Occurrence. Although it was the impression of most observers that rheumatic fever is less prevalent and less severe now than it was 10 years ago,[1449] its importance among the rheumatic diseases was documented by the several statistical studies listed in table 2. Prevalence of rheumatic fever varied from 1.2% in Hawaiian children[418] to 1.48% in the total population of a rural community in the United States.[440] The incidence of rheumatic fever in children in Great Britain was reported as 0.055%[421] and 0.069%,[951] as compared to 0.094% in the population of Mt. Kisco, New York,[440] and a 10-year average of 0.118% in Melbourne, Australia.[1003]

On the other hand, the prevalence of rheumatic heart disease seemed to be considerably greater. It ranged from 0.27% in California college students,[775] 0.66% in Colorado children,[1368] 2.8% among Wisconsin school children,[1699] up to 8.7% in Italian rice field workers.[1677] In this country, mortality in the five to 19 year age group due to rheumatic fever and diseases of the heart is outranked only by that due to accidents.[2278] However, deaths from rheumatic heart disease in the age group under 24 have declined in the past 30 years.[1700]

Table 2

Occurrence of Rheumatic Fever or Rheumatic Heart Disease in Various Populations

Geographic Location	Population Sampled	Diagnosis	Incidence or Prevalence (Per Cent)	Size of Sample	Reference
1. Italy	Female rice field workers	History of rheumatic fever	24.3 (prev.)	930	1677
2. Hawaii (Oahu)	Children 4 to 15, hospital admission	Rheumatic fever	1.2 (prev.)	6,083	418
3. New York, Pleasantville	Total population	Rheumatic fever	1.48 (prev.)	2,100	440
4. New York, Mt. Kisco	Total population	Rheumatic fever	0.094 incidence	2,400	440
5. Great Britain	All children, Bristol, Sheffield, Lincolnshire (reported cases)	Rheumatic fever	0.055 incidence	310,000	421
6. "Several English Counties"	Total population	"Confirmed" rheumatic fever	0.069 incidence	Not stated	951
7. Australia, Melbourne	Children (age not specified)	Rheumatic fever	0.118 incidence	Not stated	1003
8. California	College students	Rheumatic heart disease (chronic)	0.27 (prev.)	11,096	775
9. Colorado	62 per cent of all 6th grade children in Colorado	Rheumatic heart disease	0.66 (prev.)	11,236	1368
10. Wisconsin	7th grade children	Rheumatic heart disease	2.8 (prev.)	893	1699
11. Italy	Female rice field workers	Rheumatic heart disease	8.7 (prev.)	930	1677
12. Hawaii	Males 19 to 25	Rheumatic heart disease	1.91 (prev.)	5,419	1963

Predisposing Factors Governing Incidence. *Season.* Again, the highest incidence of rheumatic fever has occurred in the winter and spring months in the United States [1090] and in Great Britain.[317] On the west coast of the United States the peak incidence occurred in January.[281] In Hawaii, the peak months were March and July.[418] No seasonal pattern of incidence was observed in Australia.[1003]

Social and Hygienic Factors. It was emphasized again that rheumatic fever is most prevalent where living standards are low, nutrition is poor and housing crowded.[1413, 1677] In New Haven, Connecticut, the mortality rate from rheumatic heart disease was highest in the area with the lowest per capita income.[1700] It was inferred from several studies [822, 951] that an environment which favors spread of hemolytic streptococci is a determining factor in the incidence of rheumatic fever. This concept was examined directly in Melbourne, Australia. In 1,469 cases of rheumatic fever, the social distribution of the disease correlated with the social distribution of streptococcal infection, as determined by throat culture and by the frequency of positive skin tests.[1003] The low occurrence of rheumatic fever in Puerto Rico, where poverty-stricken conditions exist, was cited as evidence that poor nutrition is not the sole factor operative in the etiology of rheumatic fever.[281, 317]

Family, Heredity and Constitution. The impression that hereditary susceptibility plays some role in the occurrence of rheumatic fever has received further support in recent years.[1962] Familial rheumatic tendencies have been reported in England [255, 317, 640] and in the United States.[440] Detailed statistical analysis of 593 cases of rheumatic fever in England yielded no evidence that some families are more prone than others to develop the disease.[951] From a study of 513 families in Ireland in which rheumatic fever occurred, it was concluded that inheritance played a major role in determining familial aggregation of cases, but a mendelian mechanism could not be established.[2046]

A careful study of the families of 40 rheumatic and of 30 nonrheumatic children over a 10 to 20 year period showed high prevalence of rheumatic fever in the families of the rheumatic children, whereas in the families of the nonrheumatic patients, rheumatic fever was relatively rare. In the first and second generations of the rheumatic families, 93 cases of rheumatic fever and/or rheumatic heart disease were found, as compared with nine cases in the nonrheumatic families. The facts suggested that heredity, if a factor, does not follow a specific genetic mechanism.[822] Other workers arrived at the same conclusion.[2152] It was suggested that "inherited susceptibility" may be a genetically determined alteration in host response to repeated streptococcal infections.[1711] A significantly greater per cent of parents and siblings of rheumatic fever patients were found to have low serum concentrations of nonspecific hyaluronidase inhibitor as compared with normal controls.[7] Some of the problems in the execution and interpretation of genetic studies of rheumatic fever were presented.[52, 2046]

Sex. Most authors have agreed that rheumatic fever is evenly distributed between the sexes. Exceptions to this view cited a preponderance in males,[1090] or females.[421, 440]

Age. The mean age of first attack in one American study was 10.4 years, with an age range of four to 16 years,[1090] whereas in 360 cases reported in Great Britain the peak incidence occurred between 10 and 14 years of age.[421] One male was reported with an initial episode of rheumatic pericarditis at the age of two and one-half years.[677] Five other children with onset of rheumatic fever at age two, and two at age one, have been reported.[1312]

Race. Rheumatic fever occurred in many races. In Hawaii it appeared in 12 different racial combinations.[418] In the Connecticut study no significant difference was found between the incidence in Negro and white children.[822]

General Clinical Data and Relative Incidence of Clinical Manifestations. The incidence of various clinical manifestations of rheumatic fever, as reported in several series of cases,[289, 418, 888, 973, 1090, 1409, 2320] did not differ significantly from that noted in previous reviews. Fever was the most common manifestation, and during the acute phase ranged from 100 to 103° F. rectally when the patient was not getting salicylates.[2185] The temperature usually returned to normal after two or three weeks. Hyperpyrexia was occasionally encountered and, while it usually indicated a poor prognosis, one 20 year old man with fever of 110° F. (rectal) and cerebellar damage recovered.[460] Joint involvement was the second most common manifestation, and was present in from 41.0 to 91% of cases reported. Joint pain may be the only symptom, although usually there is swelling and sometimes redness and heat. Joints are usually involved in a migratory polyarticular manner, but mono-articular involvement occurred.[418, 2185] Aching of the muscles of legs and arms was also noted.

The exact incidence of carditis, the most serious of the rheumatic fever manifestations, was difficult to ascertain. Connor and Yoshina reported cardiac murmurs in 75% of 73 cases.[418] Bland and Jones found carditis in 65% of 1,000 cases.[202, 203] Pericarditis was less frequent, occurring in only 4 to 13% in these series. The signs and symptoms of carditis may be minimal. Arrhythmias, disproportionately accelerated pulse rate, enlarged heart, congestive failure and characteristic murmurs assisted in the diagnosis.[231] Incidence of congestive failure ranged from 5.5% to 20.7%.[202, 418] Rheumatic carditis was emphasized as a cause of death during pregnancy.[334] [In our own experience this is quite infrequent.—Ed.]

Among the other manifestations were fatigue and pallor. Abdominal pain was sometimes present and occasionally simulated an acute surgical condition.[1729] Erythema marginatum, consisting of evanescent flat or occasionally raised erythematous annular lesions, usually present over the inner surfaces of the arms and legs and on the abdomen, was considered highly suggestive of active rheumatic fever.[2185] [This lesion is generally accepted as diagnostic of rheumatic fever.—Ed.] Subcutaneous nodules usually appeared later in an acute attack of rheumatic fever in the 5 to 20% of patients who developed them.[1639] Erythema nodosum was said to occur in some cases of rheumatic fever.[143, 717] Behavior changes occurred in 52% of a recent series.[1090]

Rheumatic pneumonitis occurred in 4% of one series.[418] In nine cases reviewed,[2144] dyspnea and cough most often appeared suddenly within months of onset of rheumatic fever; pleurisy was present in a few cases. Although most of the patients in this series died, others considered that the pneumonitis was usually evanescent.[1729] Nephritis in rheumatic fever was reported again, although most observers found this lesion but rarely. Rheumatic fever was clearly demonstrated to interfere with normal growth.[960, 1096] The anemia of rheumatic fever was shown to be of the normochromic-normocytic type.[383]

The "Postcommissurotomy syndrome" received increasing attention.[162, 1064, 1982] This syndrome, characterized by fever, chest pain and cough, appeared from 10 days to several months postoperatively in as many as 30% of patients subjected to commissurotomy for chronic rheumatic valvular disease. Hemoptysis has been included, as well as arthralgia and myalgia. Pericarditis was often present. [Although the C-reactive protein and the sedimentation rate are usually elevated during the acute phase of the syndrome, the antistreptolysin O titer is usually normal.—Ed.] Most patients responded to salicylate therapy. A few were treated with corticosteroids.[1982]

Pathology of Rheumatic Fever

Cardiovascular. Study of the cardiac lesions of rheumatic fever in living patients has been permitted by the development of surgical procedures for the correction of valvular disease. Microscopic examination of amputated left auricular appendages obtained at mitral commissurotomy revealed lesions considered characteristic of rheumatic fever in 32 of 43 cases. Nonspecific fibrous thickening, with or without round cell infiltration, was noted in the epicardium. In many, the myocardium demonstrated hypertrophy of muscle fibers, perivascular scarring, and cellular infiltrations characteristic of rheumatic fever. The endocardium in many instances was thickened, with Aschoff bodies located in the subendocardial area.[1825] A similar report of 18 patients operated upon for mitral stenosis in Sweden showed comparable lesions.[192] In still another study of 25 auricular appendages, many lesions appeared active in tissue from clinically quiescent patients.[337]

A study of the cardiac tissue of 22 patients who died of acute rheumatic heart disease strongly suggested that a nonspecific myocarditis rather than Aschoff lesions alone may be responsible for the functional and electrocardiographic changes in rheumatic heart disease. Parenchymatous changes consisting of degeneration of muscle fibers were observed in 18 cases; serous inflammation occurred in four cases.[1837]

Rheumatic lesions described in coronary arteries consisted of "collarettes" of Aschoff cells, with or without obliterative arteritis. Also included in the vascular lesions was rheumatic aortitis with scarring in the media and adventitia of the aortic vasa vasorum, leading to alterations in the aortic intima and even to aneurysmal dilatation.[1729] A relationship between leukocyte-platelet thrombi in small coronary arteries and the development of Aschoff bodies was pointed out.[2042]

Since pigs are considered not to be susceptible to rheumatic fever, the finding of old healed endocarditis in 10% of 1,650 porcine hearts was cited in criticism of the tendency to consider all mitral stenosis in man as being due to rheumatic heart disease.[1838]

Joints. In a study of the synovia from a variety of rheumatic diseases, Cruickshank reported specimens from one elbow and nine knees of rheumatic fever patients. In two joints the synovium was considered normal. In the other eight the specimens showed varying degrees of congestion, with hyperplasia of synovial cells, patches of necrosis and round cell infiltration.[459]

Lungs and Pleura. Rheumatic pneumonitis was stated to occur as transient migratory areas of involvement.[1729] In a review of nine cases with rheumatic pneumonitis the pathologic changes were listed as: (1) fibrous exudates in the alveoli and occasional hyaline pseudomembranes, (2) necrosis of alveolar walls, (3) arteriolitis resembling periarteritis nodosa, (4) focal inflammatory infiltrates, usually mononuclear, and (5) granulomas (Masson bodies).[2144]

Subcutaneous nodules. Studies of subcutaneous nodules centered around attempts to characterize the chemical composition of the central core of eosinophilic fibrillar material, usually termed "fibrinoid" because of its histologic resemblance to fibrin. Histochemical studies indicated that fibrinoid differed from fibrin in its fibrillar structure, its staining after silver impregnation, and its resistance to tryptic digestion. It differed from collagen by virtue of its

argyrophilia and its strongly positive periodic acid Schiff reaction; these characteristics were lost following removal of polysaccharide. It was concluded that fibrinoid change is brought about by infiltration of collagen with a polysaccharide-rich material, possibly a glycoprotein.[770]

Ingenious parallel chemical analyses of subcutaneous nodules utilizing paper chromatography and iontophoresis indicated a composition comparable to normal subcutaneous tissue with respect to collagen and elastin, plus a tyrosine-rich substance and polysaccharide. The analyses indicated that the presence of large quantities of tyrosine in the nodule was improbable. The predominant polysaccharide constituents of the nodules and of normal subcutaneous tissue were rich in galactose and glucosamine.[420] [The results should be compared with studies of the chemical nature of fibrinoid isolated from subcutaneous nodules of patients with rheumatoid arthritis, using somewhat different methods.[185]—Ed.]

Laboratory Data

Electrocardiographic Studies. Serial electrocardiograms were necessary to document transitory cardiac disorders which occur in many patients with rheumatic fever.[724] Electrocardiographic changes in rheumatic fever were itemized as follows: (1) increased P-R interval (at least 0.04 second longer than normal value for the individual); (2) alteration in the configuration of P waves; (3) QRS slurring, notching, widening, or lowered voltage; (4) T-wave and ST alterations, and (5) increased QT_c interval.[839]

The QT_c interval (QT interval corrected for heart rate) has been considered by many observers to be useful in following the course of the disease.[2106] In 21 of 25 patients with rheumatic carditis, Solomon and Zimmerman reported the QT_c interval to be longer than 0.422 second at least once in the course of the disease; in their control series only 8% had values above this level.[1983] Of 36 patients with acute rheumatic fever, 84% had a QT_c of greater than 0.24 second.[1091] Other observers have been quite unenthusiastic about this measurement as a diagnostic aid in rheumatic heart disease. It was found to exceed the maximal normal value in only eight out of 68 electrocardiograms of children with acute rheumatic fever, and in only three of 24 with active carditis.[267] Finkel and Baldwin observed 208 children with acute rheumatic fever or chorea and noted that a significant number had a QT_c interval high enough to be of some diagnostic help, but pointed out that the levels may also be elevated in otherwise normal children.[653]

Sedimentation Rate and Alterations in Serum Proteins. The erythrocyte sedimentation rate continues to be the most popular laboratory method of following the course of the disease. Many methods for its determination are currently in use. The increase in sedimentation rate again was attributed to changes in the plasma proteins.[592] Early in the course of rheumatic fever, albumin fractions were usually decreased and alpha globulin was increased. The level of gamma globulin at times was also elevated.[285]

Acute Phase Reactants. It has become popular to refer to a large group of nonspecific materials which appear as abnormal constituents or in abnormal amounts in the blood of rheumatic fever patients during the active disease as "acute phase reactants." The C-reactive protein is present during the acute phase and disappears when activity subsides. It is believed by some to be a more sensitive and reliable index of rheumatic activity than the erythrocyte sedimentation rate.[962, 1402, 2054] [It is not specific for rheumatic fever.—Ed.]

Serum nonglucosamine polysaccharides were reported to be elevated in 55 of 57

rheumatic fever patients studied during the acute phase.[1119] Serum hexosamines were found elevated in 37 of 40 acutely ill rheumatic fever patients, whereas 37 of 40 patients with inactive rheumatic fever had normal serum hexosamine levels.[1120] The serum mucoproteins were found to be consistently elevated in acute rheumatic fever, and the level was noted to fluctuate with the clinical course of the disease in patients treated by salicylates and bed-rest. Even when patients were treated with ACTH, the mucoprotein levels did not drop immediately to the normal range, suggesting that these levels might serve as an index of disease activity in ACTH-treated patients.[1122] Another acute phase reactant was responsible for the formation of turbidity when serum from an acute rheumatic fever patient is mixed with quaternary ammonium salt.[1059]

The serum diphenylamine reaction, resulting in an intense purple color when acute phase serum is used, was evaluated in 107 patients with rheumatic fever of different degrees of severity and was found to reflect the activity of the disease by the depth of the color developed.[80] A serum mucoprotein has been found to be responsible for this color reaction. In 62 patients with rheumatic fever there was good correlation of this test with the sedimentation rate.[382]

Antistreptolysin O and Antihyaluronidase. The antistreptolysin O test has been used frequently in the diagnosis of rheumatic fever. It was suggested that its greatest value is in ruling out rheumatic fever when the test is negative.[998] In 56 patients with active rheumatic fever, 95% had antistreptolysin O titers of 250 units per milliliter or higher. In contrast, 60% of 39 patients with streptococcus infections and 42% of 45 patients with inactive rheumatic fever had similar titers.[264] [An elevated titer is characteristic of, but not diagnostic of or specific for, rheumatic fever.—Ed.] In 10 of 11 patients with acute rheumatic fever the antihyaluronidase levels were elevated above normal.[2057] This test also is not specific for rheumatic fever.

Other Studies. In a rather intricate study involving the intradermal injection of hyaluronidase and the later injection at varying intervals of a hemoglobin indicator solution into the same and control sites, it was shown that the reconstitution of hyaluronic acid in the skin of six of seven individuals with rheumatic fever was delayed. In most instances, the test reverted to normal treatment with ACTH, cortisone or salicylates.[320, 980] The finding of an excessively large "radiosodium space" in two patients with rheumatic fever led to the postulation of an increased permeability of cell membranes in this disease; this abnormality also appeared to be reversed by salicylates.[16]

Relationship of Rheumatic Fever to Other Diseases

Rheumatoid Arthritis. The relationship between rheumatic fever and rheumatoid arthritis still makes interesting conjecture. In a comparison between a series of 100 rheumatoid arthritis patients and 100 control patients, a family history of rheumatic diseases (either rheumatoid arthritis or rheumatic fever, or both) was obtained in 5.3% of relatives of rheumatoid patients and in only 2.3% of the controls.[115] Heart disease indistinguishable from that of rheumatic fever was found to occur in 10 to 15% of rheumatoid arthritis patients examined at necropsy. This represents a prevalence twice that found in the general population.[1976] In a follow-up examination of 91 patients nine to 24 years after hospitalization for rheumatic fever, 44 had joint complaints, and in 34 these dated from the illness with rheumatic fever. In only six were there objective findings justifying a diagnosis of rheumatoid arthritis; three of these dated the onset from their rheumatic fever, and three had experienced the onset at a later date.[63]

Subacute Bacterial Endocarditis. Subacute bacterial endocarditis occurred in from 1.3% to 2.6% of rheumatic fever patients.[202, 418] Antibiotics have greatly reduced the hazards of this disease. The coexistence of both diseases in their active phases was reported.[1562]

Acute Glomerulonephritis. In an epidemiologic study, Rammelkamp, Weaver and Dingle[1712] found that glomerulonephritis followed infection with specific types of streptococci; in recent years type 12 predominated, but other studies implicated types 2, 4, 18 and 31. Attack rates varied considerably. Rheumatic fever, on the other hand, was not related to a specific type of streptococcus and occurred at a fairly constant rate of about 3% in patients with any type of Group A beta-hemolytic streptococcal infection. Other differences of possible pathogenetic significance included the latent period between the infection and the clinical manifestations of rheumatic fever, the fact that rheumatic fever occurs at a later age than nephritis, and the absence of a familial factor in nephritis.[1709, 1712]

Erythema Nodosum. In an excellent review of this condition in children, Doxiadis evaluated the evidence for a relationship between erythema nodosum and rheumatic fever. He concluded that, although both conditions may be related to streptococcal infections, there is no high degree of association of the two diseases with each other.[549]

Diagnosis

The range of symptoms in some patients with rheumatic fever and the paucity of symptoms in others admit a wide spectrum of diseases in the differential diagnosis.[1286] In considering the problem of diagnosis when the full blown picture with joint pain is not manifested, Mulcahy[1511] placed the emphasis on clinical findings: "A full knowledge of the signs and symptoms of active rheumatic carditis is of far greater importance than the most extensive series of special investigations." The acute, fulminating, fatal form of rheumatic fever in an adult has been reported.[907] The diagnostic criteria consisting of major and minor manifestations as described by Jones were again listed.[71, 839, 1806]

Among the important diseases to be considered along with the diagnosis of rheumatic fever is rheumatoid arthritis.[1963] The migratory nature of the arthritis of rheumatic fever usually assists in the differentiation. Furthermore, the fever is usually higher than that of rheumatoid arthritis. The history of an acute streptococcal infection suggests rheumatic fever. When nodules are present, large ones usually suggest rheumatoid arthritis. In children, the presence of large lymph nodes suggests juvenile rheumatoid arthritis.[839] Other diseases which may simulate acute rheumatic fever include systemic lupus erythematosus, subacute bacterial endocarditis, gonorrheal arthritis, Reiter's syndrome, tuberculosis, brucellosis and infectious mononucleosis.[839, 1056] Leukemia sometimes occurs without typical blood changes, in which instances the bone and joint pain and the anemia may be confused with rheumatic fever.[551] In an adult, monocytic leukemia presented as an acute polyarthritis, with swelling and effusion in several large joints; at autopsy, the synovium of the ankle joint was found to be heavily infiltrated with leukemic stem cells.[967]

Severe erythema nodosum can closely simulate rheumatic fever; such a case, presumably tuberculous in etiology, presented arthritis, carditis and sudden cardiac death.[2161] It has been stated that rheumatic fever may be confused with endocardial fibro-elastosis.[1312] Sickle cell anemia may also resemble rheumatic fever in a Negro, since the disease is often associated with joint pains and, indeed, cardiac murmurs.[821]

Course and Prognosis of Rheumatic Fever

In general, patients with rheumatic fever survived the first attack, although recurrences were the rule. The younger the patient at the time of his first

episode, the greater the likelihood of recurrent carditis.[1056] The excellent 20 year follow-up report of 1,000 rheumatic fever patients by Bland and Jones offers some encouragement. Seventy per cent of these patients were alive at the end of the 20 years, and 56% of them had little or no limitation of their activity. Among the 653 patients with well developed rheumatic heart disease, signs of heart disease disappeared in 16% during the 20 years.[202, 203] [Many of the previously published reports on prognosis in rheumatic fever were based on necropsy studies, and hence were weighted in an unfavorable direction.—Ed.] Certain findings in this series of patients appeared to influence the final outcome. Of 277 patients who had markedly enlarged hearts or congestive failure during the acute episodes, about 80% were dead after 20 years (most within the first 10 years). Carditis carried the most serious prognosis. Pericarditis occurred in 13% of all the patients; of these, 63% were dead in 20 years. Chorea occurred in 518 patients, and 12% of these died during the 20 year period. Pregnancy during acute rheumatic fever has been said to carry a severe prognosis.[1015] It is interesting that, in the group of 1,000 patients reported above, there were 421 children born to the 709 female patients studied, with only minimal complications.[202, 203]

Scandinavian workers succeeded in obtaining follow-up information on 97% of 194 patients, nine to 24 years after they had been hospitalized for acute rheumatic fever. Sixteen had died during hospitalization, and of 23 who died subsequently, three had definite rheumatic heart disease and six had possible rheumatic heart disease. The over-all incidence of definite rheumatic heart disease in the 173 patients traced after hospitalization was 15 (9%), and of possible heart disease, 10 (6%).[65]

Mortality. Of the 1,000 patients in Bland and Jones' report, 301 died during the 20-year follow-up period. Eighty per cent of the 301 died of rheumatic fever and congestive failure; 10% of bacterial endocarditis (both acute and subacute); and the other 10% died of various causes, many unrelated to rheumatic fever.[202, 203] Of 73 patients studied by Connor and Yoshina,[418] 5% were dead within two years. Sudden death due to carditis was reported.[776]

Recurrences. In the Bland and Jones series, 23% of the living patients had recurrences in the first year and again in the second year of the follow-up period. The recurrence rate gradually fell to 8% of the living patients in the tenth year and only 1.5% in the sixteenth year follow-up.[202, 203] In the Hawaiian series of 73 cases, there were recurrences in 22% within two years.[418]

Etiology and Pathogenesis

Additional reports appeared in support of the concept that the beta hemolytic streptococcus, Group A, is the most important factor in the causation of rheumatic fever.[315, 317, 421, 523, 1407, 2213] Most studies of social, hygienic and familial factors emphasized the importance of those conditions which favored the spread of streptococcal infections. [Details are indicated in a previous section, "Predisposing Factors Governing the Incidence of Rheumatic Fever."—Ed.] From studies of the epidemiology of the disease in the Armed Forces, it was concluded that altitude, seasons, crowding, economic factors and age affect the incidence of rheumatic fever only because they influence the incidence of streptococcal infections.[1711] The historical development of current ideas about the hemolytic streptococcus and its relationship to rheumatic fever were reviewed by Fearnley.[640]

He pointed out that during World War II the carrier rate of Group A streptococcus among healthy troops paralleled the incidence of rheumatic fever. In military personnel, about 3% of persons who developed infections with Type A beta hemolytic streptococcus later developed rheumatic fever.[1711, 1712] In families, the spread of rheumatic fever appeared to pass through the same generation from the oldest child to the next youngest.[822]

McCarty[1407] devoted particular attention to those "random cases" of acute rheumatic fever in which the hemolytic streptococcus was not obviously implicated. Reports of other "precipitating factors" failed to rule out streptococcal infection, or failed to distinguish recrudescence of rheumatic fever from new attacks. The streptolysin O response in such "random cases" was identical with that of patients who developed rheumatic fever after known streptococcal infection.

Additional experiments were reported on the production of rheumatic-like lesions in various tissues by the administration of Group A streptococci or their products.[1192] Following repeated Group A streptococcal subcutaneous infections in rabbits, typical Aschoff bodies appeared in the heart. Evidence was presented that these Aschoff bodies were derived from myocardial muscle fibers.[1516] Carditis which developed in rabbits after repeated injection of Group A streptococci and/or their products was thought to be dependent upon an immune state in the animals.[1778]

The mechanisms by which streptococcal infection produces the clinical manifestations and pathologic lesions of rheumatic fever continued to elude investigators. There was little evidence that the serologic type of the streptococcus or location of the disease it produces is an important factor in determining the attack rate.[1711] Many favored the concept of hypersensitivity, or at least altered reactivity, on the part of the host. The antistreptolysin O response following hemolytic streptococcus infections in early childhood was found to exhibit three different patterns of response: (1) in the very young children, the titers tended to be very low; (2) in the slightly older age group, the titers were higher but poorly maintained; and (3) in the still older age group, there was a vigorous and well maintained antistreptolysin O titer following infection. The authors proposed that the immune response mechanism, as measured by antistreptolysin O titers, requires conditioning with repeated infections before prolonged, elevated titers can be achieved. Since children with rheumatic fever exhibit the third type of response, there may be some relationship between the pathogenesis of rheumatic fever and this active antibody response mechanism.[1717]

It was found that the precipitin reaction for streptococcal carbohydrate may occur in the serum of patients in the absence of streptococcal infection, and that the absence of this reaction does not rule out streptococcal disease.[2223] Speculation linked the exudative pharyngitis as source of antigen to the heart as the chief "shock organ" through the venous and lymphatic connections. "It is tempting to assume that in those children who develop carditis after streptococcal sore throat, the inflamed pharynx and cardiac tissue are linked together by a direct lymphatic pathway."[1257] Provocative studies by Glynn and Holborow[769] suggested the possibility that streptococci may produce auto-antibodies to normal connective tissue constituents. When hemolytic streptococci were grown in the presence of chondroitin sulfate, the product produced antisera in rabbits which gave a precipitin reaction with the polysaccharide alone. Of six rabbits so immunized, five developed synovitis [but apparently no carditis. Attempts to confirm these observations have been unsuccessful.—Ed.]

There were further studies of rheumatic-like lesions produced in rabbits by hyper-

sensitivity to horse serum. This response could not be potentiated by adding killed streptococci to the serum, but some protection of the animals was afforded by histamine desensitization.[1178] [Studies of the effect of adrenal steroids on this reaction are reviewed in the section on the "Adrenals and Rheumatic Diseases."—Ed.]

The lack of direct experimental evidence for the hypersensitivity theory of rheumatic fever was emphasized by MacLeod, who postulated that rheumatic lesions may result from direct attack upon tissues by group A streptococci or their toxins.[1357] Other possible factors in etiology and pathogenesis received scant attention. The possibility of virus etiology was mentioned only as an untested idea which may warrant investigation.[640] The only dietary factor implicated in the studies reviewed was protein intake; both inadequate dietary protein and antecedent upper respiratory infections were correlated with the incidence of rheumatic fever in Italian rice field workers.[1677]

Studies of adrenal cortical function in patients with rheumatic fever provided little support for the concept that hormonal factors are important in the development of the disease. Patients with rheumatic fever did not differ significantly from control subjects with respect to the plasma levels of 17-hydroxycorticosteroids before and after ACTH stimulation,[608, 1707] the urinary excretion of phosphomolybdate-reducing steroids and 17-ketosteroids,[1878] and the magnitude of induced eosinopenia.[2244] Although cardiac lesions were produced by the administration of large doses of desoxycorticosterone acetate to unilaterally nephrectomized rats, the lesions differed from those of rheumatic fever and appeared to result from potassium depletion.[1641]

Conclusions Regarding Etiology. There seems to be little doubt that rheumatic fever follows in the course of some infections with group A hemolytic streptococci. The reasons why approximately 3% of such infections lead to rheumatic fever are not clear; present information suggests that the important determining factors reside in the person affected, possibly in the form of altered immune reactions, rather than in the type specificity of the infecting agent. The problem of inherited susceptibility requires further clarification. The factors responsible for localization and perpetuation of the rheumatic process are also unsolved problems.

Treatment of Rheumatic Fever

Rest and Convalescent Care. The principles of these aspects of treatment, discussed in previous reviews, were reiterated.[1929] When 50 children with rheumatic fever were interviewed to determine their attitude toward the disease and its required treatment, it was found that, in general, they did not resent restrictions in institutions where other children were receiving similar treatment. While they were more aware of restrictions at home, readjustment to home life usually offered no special problems.[119] After following 45 patients cared for at home for 30 months, Young and Rodstein concluded that, provided certain initial criteria for home suitability are met, most children with active rheumatic fever free of congestive heart failure can be cared for as well at home as in the hospital, "with equally good end-results and with greater over-all advantage to the patient and his family."[2300]

Salicylates. The difficulties encountered in critically evaluating the therapeutic potency of anti-inflammatory agents (salicylates, cortisone and corticotropin) in rheumatic fever were carefully analyzed and fully discussed by Fischel, Frank and Ragan.[655] To overcome these difficulties, they suggested study of (1) the response of the local and systemic manifestations of rheumatic

inflammation in the patient with chronically active rheumatic fever whose course prior to therapy has been stable, and (2) the response of the patient during and after treatment who, upon premature withdrawal of a therapeutic agent, manifests a rebound in rheumatic manifestations.

Fischel contended that salicylates possess not only analgesic and antipyretic but also anti-inflammatory properties, citing supporting experimental, clinical and laboratory evidence. Moreover, when salicylates were prematurely discontinued, rebound of manifestations of inflammation followed after an interval of several days. He believed that carditis may be suppressed in the majority of patients when salicylates are introduced early in the course of the disease. He urged that salicylates be administered over a prolonged period, and that they be continued during cautious re-ambulation of the patient and discontinued not sooner than several weeks or months after all signs of rheumatic activity have subsided. Dosage to the point of mild toxicity (tinnitus) was recommended, with subsequent slight reduction to the point of tolerance.[654] [In severe cases, especially in children, toxicity may develop sooner than satisfactory control of manifestations is achieved. Steroid therapy offers a practical advantage in such cases.—Ed.] No special benefit was to be gained by using parenteral routes of administration or by blocking excretion with such agents as para-aminobenzoic acid.[654] During administration of sodium salicylate, magnesium trisilicate or aluminum hydroxide gel tablets were found to relieve gastric distress with the same effectiveness as sodium bicarbonate, but without lowering the plasma salicylate level.[936]

Mode of Action of Salicylates. The observations that the clinical and biologic effects of salicylates mirror, albeit somewhat palely, those of ACTH and cortisone led to speculation that the therapeutic action of salicylates is mediated through the pituitary and adrenal glands.[46, 874, 1027, 1628] The occurrence of "mild Cushing's syndrome" in a patient with rheumatic fever receiving 5 gm. of aspirin daily was reported.[384]

In two independent studies using rats, sodium salicylate in doses sufficient to give plasma levels of 15 to 40 mg. per 100 ml. depleted the adrenal ascorbic acid to an extent related in a linear manner to the dose, and this effect was abolished by hypophysectomy. Such effect was not produced by aliphatic acids, but was not strictly specific for the salicylate ion.[455, 950] The ACTH titer, determined by bio-assay, was found to rise in the blood of rats very soon after the injection of about one-half the lethal dose of sodium salicylate.[574] On the other hand, antagonism between the action of salicylates and cortisone with respect to effects on carbohydrate metabolism was reported in alloxan diabetic rats,[237] in force-fed, partially depancreatectomized rats,[1045] and in rats receiving cortisone.[1956]

Investigations of the effect of salicylates on the circulating eosinophils in humans have yielded conflicting results. Roskam and Van Cauwenberge[1807] reported definite eosinopenia in five to 12 hours after oral administration of 4 to 6 gm. of salicylates, but Meade and Smith[1438] found no significant depression in eight patients receiving doses of salicylate sufficient to provide plasma levels of 38 mg. per 100 ml., or of gentisate providing levels of 35 mg. per 100 ml. The adrenocortical steroid excretion in the urine was reported to be elevated during the administration of 8 gm. of acetylsalicylic acid daily to eight subjects.[2163] [In this study, adrenocortical steroids were determined as "reducing steroids," with no precautions to avoid probable augmentation due to excretory products of the salicylates. It is significant that the 17-ketosteroid excretion of the subjects was not significantly altered.—Ed.]

It was shown that hypophysectomy and adrenalectomy did not alter the in vivo inhibitory effect of salicylates on hyaluronidase spreading factor in rats.[1628] Others

found that salicylates acted directly on the ground substance by inhibiting spreading enzymes; moreover, they found no diminished resistance to spread of hyaluronidase in rheumatic subjects as compared to normal subjects, and no greater inhibitory effect of salicylates on hyaluronidase in rheumatic patients.[78] While Ungar, Damgaard and Hummel confirmed the effect of salicylates in depleting the rat adrenal of ascorbic acid, they found that after hypophysectomy or adrenalectomy, salicylates still inhibited the inflammation produced by the passive Arthus' reaction in rabbit joints. They concluded that the anti-inflammatory action of salicylates was not exerted through pituitary-adrenal stimulation, and suggested that it was exerted at the tissue level by inhibition of "fibrinolysin."[2156] [The above observations can be evaluated as follows: Evidence that salicylates can stimulate the pituitary adrenal system in experimental animals is quite convincing, although it appears that salicylates mimic the hormonal effects only partially. Evidence that salicylates exert their suppressive effect on experimental inflammatory processes through a hormonal mechanism is at least controversial. Evidence that humans receiving therapeutic doses of salicylates manifest any evidence of adrenocortical stimulation is most unconvincing. Evidence that salicylates exert their therapeutic action in the rheumatic diseases through stimulation of the pituitary-adrenal system is totally lacking.—Ed.]

It was suggested that the therapeutic action of hydroxybenzoic acids such as salicylic, gentisic and γ-resorcylic acids depends on the chelate ring formation. γ-Resorcylate was found to possess about 10 times the antirheumatic potency of salicylate in patients with rheumatic fever, but its undesirable effects were so severe as to render it of little practical usefulness. Isomers of salicylate which do not chelate had no antirheumatic activity.[1732] Recent advances in the pharmacology of salicylates were reviewed.[1957]

Metabolism and Toxicity of Salicylates. After ingestion of 0.65 gm. of aspirin, measurable salicylate levels were obtained in the blood in 10 minutes, and concentrations of 5 mg. per 100 ml. were reached in one hour. Thirty per cent of the blood salicylate remained acetylated.[1955] The serum level of gentisate reached a maximum two hours after ingestion of sodium gentisate. The serum level was not related to body weight but did vary inversely with the fluid intake. Sodium bicarbonate increased the absorption and decreased the excretion of gentisate, as reflected by plasma levels at four-hour intervals. No alteration of urine excretion was produced by ammonium chloride or potassium citrate.[1439]

The three stages of salicylate toxicity described in the Tenth Review—respiratory alkalosis, compensated metabolic acidosis and, finally, decompensated acidosis due to glycogen depletion and accumulation of acetone bodies—were again described.[541, 730] The reported cases of aspirin poisoning were listed.[1824] Three additional cases showed the usual manifestations of hyperpnea, profuse sweating and collapse.[730, 1824, 1885] One patient showed also vomiting, dilated pupils and ecchymoses.[1885] Unexplained hyperpnea is the sign that first suggests the correct diagnosis, which can be readily confirmed by analysis of blood and urine for excess salicylates. Hydration and correction of acidosis are the important principles in combating toxicity. One study indicated that salicylates are removed much more rapidly by hemodialysis (artificial kidney) than by the normal kidney.[541]

Isolated reports of bleeding attributed to aspirin continued to appear. Intestinal bleeding for eight years, apparently due to ingestion of 3 gm. of aspirin a day, was reported. Although the patient had intestinal lesions (polyp, hiatus hernia, carcinoma of colon) which were originally thought to be sources of blood loss, it was demonstrated by interrupting aspirin administration repeatedly that the bleeding occurred only during periods when aspirin was taken.[1481] In another patient with hemorrhage after tooth extraction, continued bleeding related to ingestion of aspirin was attributed to a combination of prothrombinopenia and increased capillary fragility; it was prevented by addition of vitamin K.[1951] In a third patient, a 78 year old, hemorrhage in mouth, lips and face and under the skin was associated with low prothrombin levels.

The abnormalities disappeared when aspirin medication was stopped, and recurred on resumption of the drug. There was some impairment of liver function.[1630] [Such cases are difficult to understand, since systematic studies have indicated that the prothrombin level is not altered by salicylates unless the plasma concentration reaches toxic levels. The possibility cannot be excluded that, rarely, smaller doses of salicylates may contribute to a bleeding tendency. The frequency of this danger does not seem great enough to justify the routine addition of vitamin K to salicylate medication.—Ed.]

Cortisone and Corticotropin. The striking effectiveness of adrenal cortical therapy on the manifestations of rheumatic fever, summarized in the Tenth Rheumatism Review, was amply confirmed in numerous papers published during the period of this Review. Disagreement, however, centered on two major problems: Is hormonal therapy distinctly superior to the use of salicylates in (a) controlling the manifestations of acute rheumatic carditis, and (b) in preventing the later development of rheumatic heart disease?

Reports on the evaluation of adrenal cortical hormone therapy in rheumatic fever may be divided into three groups according to their conclusions: (1) Cortisone or corticotropin is of real value and may in some cases be lifesaving;[57, 84, 106, 148, 270, 271, 754, 834, 840, 1121, 1302, 1722, 1892, 2171, 2262, 2263, 2282] (2) the effects of the hormones are beneficial, but judgment should be reserved as to their influence on the natural course of the disease, ultimate cardiac damage or valvular deformities;[170, 304, 544, 826, 1218, 1219, 1508, 2299] and (3) cortisone or corticotropin is of doubtful value, or at least is *not* distinctly superior to salicylate.[232, 319, 347, 1082, 1083, 1115, 1118, 1816, 1908] In patients with protracted, smouldering, active carditis, exudative phenomena were suppressed but there was no clear-cut effect on the proliferative phase of the cardiac involvement.[106, 2105] Rheumatic pneumonitis responded to ACTH in two patients,[348] but was not completely controlled in a third.[1909] The development of fatal constrictive pericarditis following treatment of rheumatic pericarditis with ACTH was described.[1892]

In the above reports there was wide range with respect to dosage and duration of hormone administration, and much variation as to the time from onset of the rheumatic episode at which hormonal therapy was introduced. Two series offered controlled observations. Johnson and Ferencz compared their experience in 100 patients treated with cortisone against 80 patients treated before cortisone became available. The two series were comparable with respect to incidence of cardiac damage at time of treatment, and evidence of prior rheumatic heart disease. They noted "no significant difference in the incidence of heart disease after the treated episode in the cortisone and pre-cortisone series," and concluded that the chief value of the steroid was in the extremely ill patient with rheumatic carditis.[1082] Rowe, McKelvey and Keith found no significant differences in the effect on the carditis in an interspersed series of 41 cases divided into roughly equal groups receiving salicylates, ACTH and cortisone in an arbitrary dosage.[1816] [This report constituted a portion of the coöperative study described below.—Ed.]

[Since the period covered by this Review, the results of the "clinical trial," admirably designed and meticulously executed by the Rheumatic Fever Working Party of The Medical Research Council of Great Britain and The American Council on Rheumatic Fever and Congenital Heart Disease of The American Heart Association, have become available (Circulation 11: 343, 1955). The reported series consisted of 497 children under the age of 16; by random sampling 162 received corticotropin, 167

cortisone, and 168 aspirin. The dosage schedule and duration of therapy were fixed in all cases. The patients were uniformly treated for exactly six weeks, during which time they received an aggregate of 4.1 gm. of cortisone, or 2,460 U.S.P. units of corticotropin, or aspirin in amounts that varied with the patient's body weight. Of special interest is the group of 252 cases of carditis without preëxisting heart disease. In this group 116 patients were treated during the first two weeks of illness, 82 between the beginning of the third and end of the sixth week, and 54 after the sixth week. The rate of disappearance of organic murmurs one year after the end of treatment was not significantly different among the three groups. It was concluded that "treatment with either of the hormones resulted in more prompt control of certain acute manifestations but this more rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period upon cessation of treatment. Treatment with the hormones also led to more rapid disappearance of nodules and of soft apical systolic murmurs. At the end of one year there was no significant difference between the three treatment groups in the status of the heart."

This report measured the results in relation to separate manifestations of the disease. It did not state how many patients in each group recovered without heart disease, nor did it arrange the results in relation to time from onset when treatment was begun. It is noteworthy that the question as to optimal dosage and duration of therapy was beyond the scope of this study and therefore was not explored.—Ed.]

[The importance of early treatment and adequate dosage in obtaining more favorable end results was suggested by early experiences,[106, 301, 834, 1121] and appears to be borne out by reports since the period covered by this Review. Particularly impressive were the experiences of Roy and Massell and of Markowitz and Kuttner, reported at the June, 1955, meeting of the American Rheumatism Association. Roy and Massell compared the incidence of cardiac damage at time of discharge from initial attacks in 56 patients receiving large dosage and prolonged administration. In those receiving a total of 3.1 gm. of cortisone or 1,100 to 2,500 units of ACTH over a period of six weeks, 70% had cardiac damage, as compared to 38% in those receiving an aggregate dosage of 13 to 15 gm. of cortisone, or 4,100 to 7,000 units of ACTH over a period of 12 to 16 weeks; results were distinctly better in those treated within two weeks of onset. Markowitz and Kuttner treated 40 patients in initial attacks of rheumatic carditis with oral cortisone or hydrocortisone. The aggregate dosage ranged from 10 to 30 gm., and the periods of administration from nine weeks to 12 months. After follow-up studies which ranged from six to 22 months, 83% of the 29 patients who were treated within three weeks or less of onset had normal hearts. Of the 11 patients treated later than three weeks from onset, only 19% had normal hearts.

Such experience has led to the recommendation that, to achieve the most favorable results with hormonal therapy in cases of acute rheumatic carditis, it is most important to institute treatment very early during the initial attack, to use doses that are large enough, and to maintain therapy for periods that are long enough. The optimal period to start treatment is as soon as possible after the diagnosis is made, preferably within the first two to three weeks of the disease. To be adequate, the aggregate dose should be approximately 15.0 gm. of cortisone, or 7,000 U.S.P. units of corticotropin, given over a period of 14 to 16 weeks. During the period from 1949 to 1952 the "customary" aggregate dose was 4.0 gm. of cortisone, or 2,500 U.S.P. units of corticotropin, administered over a period of six weeks.—Ed.]

Laboratory Changes Associated with Hormonal Administration. The levels of various protein and polysaccharide components of the serum, which were markedly elevated in patients with rheumatic fever before cortisone therapy, fell promptly during treatment.[592, 593, 1903] These changes closely paralleled clinical improvement, but whether this phenomenon was the result of medica-

tion or recession of the disease process was not known. Others reported that, although the hormones caused an early drop in the sedimentation rate and nonspecific hyaluronidase inhibitor, the blood mucoproteins remained elevated during the natural course of the disease.[6, 8] Following withdrawal of cortisone or corticotropin therapy, abnormal laboratory findings often reappeared. Usually they subsided in two to three weeks without further treatment, and frequently were not accompanied by recurrence of rheumatic symptoms.[2816]

Necropsy Findings After Hormonal Therapy. In two autopsied cases of chronically (six months) active rheumatic carditis treated with corticotropin and cortisone, histopathologic lesions characteristic of rheumatic carditis (Aschoff nodules, auricular endocarditis, valvulitis and pericarditis) were found.[784, 1990a] It is interesting that in one of these cases there was noted a "striking lack of cellular reaction to extensive interstitial collagen degeneration."[784] [It is noteworthy that hormone therapy was instituted three and five months, respectively, after onset of illness, and was given in interrupted courses.—Ed.]

Other Drugs. Hydroxy-phenylcinchoninic acid (HPC) as an antirheumatic agent was found to be as effective as salicylates in rheumatic fever and rheumatoid arthritis.[1736, 1934] It was noted that the improvement following administration of HPC to five patients with rheumatic fever was associated with a fall in serum hyaluronidase inhibitor and no reduction in the circulating eosinophils or urinary 17-ketosteroids.[632] Phenylbutazone was found effective in five patients with acute rheumatic fever that had not responded to salicylates.[664]

Prevention of Rheumatic Fever

The basic principles for the prevention of rheumatic fever that emerged from the papers included in the Tenth Rheumatism Review have been accorded renewed support by subsequent publications.[36, 1392a, 1491, 1708, 2055, 2188] Two principles prevail: (1) rheumatic fever may be prevented by promptly treating streptococcal infection in any patient; (2) recurrences of rheumatic fever in known rheumatic subjects may be avoided by prolonged, uninterrupted prophylaxis.

Prevention of Rheumatic Fever by Treatment of Streptococcal Infection. The symptoms, signs and laboratory changes which aid in the early diagnosis of hemolytic streptococcal infections were again reported.[36] There is ample evidence that penicillin therapy of acute streptococcal infections almost completely prevents the subsequent occurrence of acute rheumatic fever. Rammelkamp and his co-workers at the Streptococcal Disease Laboratory at the Warren Air Base in Wyoming injected intramuscularly procaine penicillin G in oil containing 2% aluminum monostearate according to one of three dosage schedules in 1,178 patients with exudative tonsillitis or pharyngitis, and compared the sequelae that occurred within the next 45 days with those in 1,162 untreated patients who served as controls. Only two cases of rheumatic fever developed in the penicillin-treated group, compared with 28 cases in the untreated group. Furthermore, penicillin therapy eradicated the streptococcus from the oropharynx and inhibited formation of antistreptolysin in the majority of patients. The most effective schedule consisted of three injections given over a 96-hour period, totaling 1,200,000 units.[2188] Streptococcal infections in rheumatic fever subjects were treated by Massell and associates with penicillin administered (orally or intramuscularly) over a 10 day period in 34 instances,

and only two recurrences of rheumatic fever developed; whereas in 12 similar but untreated infections, six attacks of rheumatic fever developed. Again the antistreptolysin response was suppressed by penicillin therapy.[1391, 1392a] No instances of development of resistance to penicillin by group A hemolytic streptococci have been encountered.[1193] Since penicillin therapy for streptococcal infections in rheumatic subjects is effective in preventing rheumatic fever, it might be reasoned by some that this measure should obviate the need for continuous prophylactic use of antibiotics. The fact remains, however, that approximately 40% of streptococcal infections produce few, if any, symptoms and therefore escape recognition.[1708] [It is now widely accepted that sulfonamides, unlike penicillin, are not effective in preventing rheumatic fever when administered after a hemolytic streptococcal infection has developed.—Ed.]

In a controlled study utilizing over 2,000 subjects with exudative tonsillitis or pharyngitis, Aureomycin was also demonstrated to be effective in reducing the incidence of rheumatic fever, in eradicating the streptococcal infection, and in inhibiting the development of antistreptolysin O. However, penicillin was superior to Aureomycin in each of these respects, and therefore is the drug of choice.[1018] The effect of time of initiation of penicillin therapy of streptococcal infections upon the immune response of the host was carefully studied. While optimal inhibition of antistreptolysin O was obtained when treatment was begun as early as possible, significant depression of antibody formation was obtained when treatment was begun as late as five days after the onset of symptoms.[272]

In the administration of penicillin for streptococcal infections, it should be remembered that almost all strains of this organism are sensitive in vitro to less than .03 unit of penicillin, and that effective blood levels should be maintained for a period of at least 10 days. The recommended doses are: (1) oral penicillin, 250,000 units three times daily for 10 successive days; (2) procaine penicillin in 2% aluminum monostearate in oil, 300,000 units for children or 600,000 units for adults, intramuscularly, immediately upon making the diagnosis and every three days thereafter for a total of three doses; or (3) benzathine penicillin (N, N′ dibenzylethylenediamine dipenicillin G), 600,000 to 900,000 units injected intramuscularly only once.[36] It was demonstrated that single injections of benzathine penicillin (a new repository preparation) were effective in eliminating the streptococcus carrier state in most cases.[2055] For patients who are sensitive to penicillin, Aureomycin, 2.0 gm. daily for six days, should be given orally. The importance of eradicating the streptococci was emphasized.[1018]

Continuous Prophylaxis for Prevention of Recurrences of Rheumatic Fever. In addition to the above measures for the treatment of streptococcal infection, which may be used for prevention of recurrences in known rheumatic subjects, continuous prophylaxis may also be employed. Convincing evidence has now been collected that sulfonamides, oral penicillin and benzathine penicillin are effective in reducing the recurrence rate significantly. Without prophylaxis, the recurrence rate was observed by Fischel to be 37% during the first year following an episode of rheumatic fever in a group of 116 subjects. Sulfonamide prophylaxis reduced the recurrence rate sevenfold as compared to controls—from 14 to 1.9%.[1710] In practical use, recurrence rates were cut, in comparison with previous experience at the same institutions, from 61% to 3.7% in Virginia (109 patients observed an average of 54 months),[300] from 26 to 5.4% in Rhode Island,[641] and from 24.7 to 0.4% in Philadelphia (252 patient-years).[1762] No differences between sulfadiazine and Gantrisin were noted with respect to effectiveness or toxicity.[300]

With the prophylactic use of oral penicillin the recurrence rate was reduced more than tenfold, from 9.1 to 0.79%,[1193] and in other series was reduced to "virtually nil."[641, 1762] The ability of oral penicillin to prevent streptococcal infections of the throat was again demonstrated.[641, 721] [The effectiveness of benzathine penicillin in preventing recurrences of rheumatic fever when injected intramuscularly once a month in doses of 1,200,000 units is affirmed in publications since the period covered by this Review. There was not a single recurrence in 145 rheumatic subjects followed for 21 months by Stollerman (Am. J. Med. 17: 757, 1954), and in 96 subjects followed for 14 months by Diehl, Hamilton, Keeling and May (J. A .M. A. **155**: 1446, 1955).—Ed.]

The recommendations for year-round prophylaxis by the Committee on Prevention of Rheumatic Fever were published widely during 1953.[36, 410] [The most recent revision by this Committee (Circulation **11**: 317 (Feb.) 1955) recommended that all individuals who have a well established history of a previous attack of rheumatic fever or chorea, or who present unquestionable evidence of rheumatic heart disease, should be given continuous prophylaxis "throughout life." One of the following three agents may be used: (1) oral sulfadiazine, 0.5 to 1.0 gm. once daily; (2) oral penicillin, 200,000 to 250,000 units once daily; or (3) benzathine penicillin G, 1,200,000 units intramuscularly once a month.—Ed.]

Community Responsibility and Public Health Services. The American Council on Rheumatic Fever has defined five general areas of community function: (1) professional services, which include physicians, medical social workers, educators, occupational therapists and rehabilitators; (2) treatment services; (3) case-finding service, in which the school health service plays an important role; (4) follow-up services; and (5) public information. Reports on the operation of a rheumatic fever program in South Carolina,[133] in Ohio[1345] and in Colorado[545] were presented. Successful implementations of community prophylactic programs were described.[1954] A picture of rheumatic fever as seen in Rochester, New York, during a short period of observation was given in detail.[1090]

[While other factors may be involved in the pathogenesis of rheumatic fever, the only practicable method of prevention is by control of hemolytic streptococcal infections. Several methods of such control are available—the remaining task is actually to put them into effect.—Ed.]

Sydenham's Chorea

The incidence of chorea in patients with rheumatic fever varied in reported series from 10%[419] to 51%.[202] The pathology of the disease was again described as a proliferative endarteritis with perivascular infiltration and cell infiltration into nerve tissue in the basal ganglia, cerebral hemispheres and brain stem.[468] Clinically, the onset of the disease is usually gradual, at first manifested by the dropping of objects and then by stumbling. Ataxia becomes more pronounced and general irritability and muscular twitching are noted. Irregular, purposeless movements are characteristic.[878] Because the disease is subject to spontaneous remissions the evaluation of therapy is difficult. To assist in such evaluation, Dixon and Bywaters used as an index of dexterity the time required for the patient to fit 100 plastic pegs into a board. Changes in this index reflected changes in the clinical state. They have also used a kinetic bed to quantitate the movements of the patients at rest.[581]

Treatment of chorea is nonspecific. Most patients recover after three or four months of illness. Rest and sedation, using phenobarbital or paraldehyde

in the more severe cases, have been advised.[2185] Cortisone was reported as beneficial in one case.[468] Corticotropin and cortisone used simultaneously were felt to be of benefit in six cases of chorea, with disappearance of symptoms in all cases in from eight to 48 days of therapy.[1859] Some reported benefit from corticotropin,[1904] but others obtained no significant result from corticotropin [531] or from cortisone.[66]

Rheumatoid Arthritis

It was estimated by the Arthritis and Rheumatism Foundation that there are 700,000 cases of rheumatoid arthritis in the United States, a figure which conformed roughly to genetic expectancy.[2011] The morbidity of rheumatoid arthritis in Denmark was estimated at 0.8 per thousand.[87]

Clinical Manifestations of Rheumatoid Arthritis

Age and Sex. Rheumatoid arthritis is a disease of the elderly as well as of the young.[344, 1607] Of 100 consecutive patients whose disease started at or after 60 years of age, one-half were male, an incidence considerably higher than that reported for other series of patients of all ages.[344] [With the increasing percentage of the population in older age groups, the long-accepted concepts of the age incidence of this disease may well have to be revised.—Ed.]

Onset of Arthritis. Variations from the typical, insidious onset of joint involvement were frequent. The onset was often acute, asymmetric, and occasionally mono-articular in patients at any age.[1089, 1137, 1607] In the older age group the onset of rheumatoid arthritis often simulated the shoulder-hand syndrome.[344, 1138] The atypical onset of rheumatoid arthritis in one or both hips was another source of diagnostic difficulty.[1245] Patients frequently dated the onset of symptoms from an injury to the affected joints; this observation led some to cite trauma as an important precipitating factor.[584, 1136, 2205] [Rheumatoid arthritis is a capricious disease and can have almost any type of onset.—Ed.]

Articular Manifestations. Ulnar deviation of the fingers, a common deformity of rheumatoid arthritis, was more often seen in women [2161] and in patients with severe disease of long duration.[1343] The patient's occupation did not appear to influence the incidence of this deformity.[1343] While some observers concluded that the degree of use of the hands is an etiologic factor,[2161] others disagreed.[1343] It was suggested that this deformity is produced by use of the hand in an abnormal manner, determined by inability to flex the proximal interphalangeal joints.[639] Most authors agreed that ulnar deviation of the fingers is the result of certain anatomic alterations, such as atrophy of intrinsic muscles of the hand, with resulting muscular imbalance;[1793] capsular and extensor tendinous swelling adjacent to the metacarpophalangeal joints, with resulting slip ulnarward of the extensor tendons off the knuckles;[1908] and relaxation of collateral ligaments.[2161] Lush concluded that the deformity was probably not due to any consistent anatomic defect.[1343]

At the wrist, it was observed that flexion contracture is most common because the dorsal ligamentous structures are much weaker than the volar, and give way more readily; ulnar deformity tends to supervene because ulnar deviation of the wrist is a functional counterpart of flexion. Metacarpophalangeal deformity was likely to follow the path set by the wrist deformity. Since wrist flexion tightened the extensor tendons of the fingers and drew the proximal phalanges into extension, hyperextension of the metacarpophalangeal joints

generally accompanied flexion deformity of the wrist. Conversely, fixed flexion of the metacarpophalangeal joints tended to be associated with extension deformity of the wrist. Interphalangeal deformities were similarly motivated. The effect of gravity was considered minor.[2036]

The shoulder joint was involved in 55 of 100 elderly patients with rheumatoid arthritis.[244] Unusual, severe involvement of the shoulder by both rheumatoid arthritis and osteoarthritis was documented by tissue obtained at operation.[1714a] Simple procedures were described by which digital swelling[906] and the mobility of joints[2252] may be measured.

Extra-Articular Manifestations. *Skin.* Cutaneous fistulae in the neighborhood of rheumatoid joints, described in two patients, were believed to drain sterile, subcutaneous abscesses resulting from the extrusion of necrotic bony fragments from severely eroded superficial joints.[318] Chronic ulcers of the leg occurred in two patients in whom splenomegaly and leukopenia were associated with rheumatoid arthritis (so-called Felty's syndrome); three cases with similar association of clinical findings had been reported previously.[1851]

Tendons and Tendon Sheaths. Spontaneous rupture of the tendon of the extensor pollicis longus was diagnosed in five of 433 patients with rheumatoid arthritis. In each case, rheumatoid arthritis was active at the time of the rupture, which was manifested clinically by sudden discomfort in the wrist or forearm and inability to extend the terminal phalanx of the thumb. Histologic alterations consistent with rheumatoid tenosynovitis, tendonitis and myositis were described in the one instance in which pathologic material was available for study.[894] Biopsies of six patients with rheumatoid tenosynovitis revealed extensive invasion of the involved tendons, muscles and surrounding tissues by a tumorous growth of cellular collagenous tissue. Between the lobules of the tumor masses, cystlike structures with fibrous walls and villous hypertrophy of their synovial lining were noted. The terms "collagenous pseudo-tumor of tendon sheaths" or "tumorous rheumatoid tenosynovitis" were recommended to describe these lesions.[1156]

Muscle. Unequivocal electromyographic evidence of muscle spasm or any other type of spontaneous electric activity could not be demonstrated in any of 25 patients with rheumatoid arthritis, thereby seeming to eliminate spasm as the cause of muscular atrophy and weakness in rheumatoid arthritis. All records revealed evidence of weak muscular contractions during voluntary effort. These observations were compatible with the theory that muscular atrophy and weakness in rheumatoid arthritis result from a central inhibitory state in the spinal cord, presumably produced by painful afferent impulses from the local lesions.[1509] [Alternative explanations, such as primary involvement or atrophy of muscle, are equally compatible with these findings.—Ed.]

Other Visceral Manifestations. Attention was drawn in the previous review to the discrepancy between the high incidence of cardiac lesions in postmortem studies of patients with rheumatoid arthritis and the scant clinical evidence of involvement of the heart during life. Electrocardiographic studies of 700 patients with rheumatoid arthritis in Sweden failed to show a higher percentage of abnormalities than was seen "in normal material."[1782] Isolated case reports of clinical evidence of cardiac involvement in rheumatoid arthritis were not convincing.[2014] [The data presented in some case reports do not permit exclusion of rheumatic fever or other "collagen disease." While heart disease is occasionally evident in patients with rheumatoid arthritis, such clinical manifestations are much less frequent than the incidence of cardiac lesions at postmortem examinations. —Ed.]

Pulmonary lesions were again described in patients with rheumatoid arthritis.[1808] Certain unusual radiologic features were noted by the Pneumoconiosis Council in Welsh coal miners who had rheumatoid arthritis. Not only was the incidence of progressive massive pulmonary fibrosis much higher in these patients than in miners without rheumatoid arthritis, but also in 25% the roentgenograms showed distinctive, well defined opacities fairly evenly distributed throughout lung fields. Both dust exposure and the presence of rheumatoid arthritis were considered factors in their production, and the possibility was considered that they may represent rheumatoid nodules.[826, 1457]

Several references were made to the ocular manifestations of rheumatoid arthritis. These included serous, nongranulomatous uveitis,[2159] scleritis or episcleritis,[357] and a more isolated, localized lesion of the sclera designated as scleromalacia perforans.[26, 2104] The frequent coexistence of rheumatoid arthritis and keratoconjunctivitis sicca was again reported.[1302, 1622, 1726, 1938] [A critical evaluation of the joint disease seen in patients with keratoconjunctivitis sicca is needed.—Ed.]

Cases of rheumatoid arthritis complicated by amyloidosis,[871, 1940] and others accompanied by splenomegaly and leukopenia (Felty's syndrome),[1406] were again described.

Special Clinical Features. There was no new, significant information which might explain the ameliorative effect of jaundice in rheumatoid arthritis. The alleged existence of "bilirubinolytic" and "bilirubin-soluble pathogens" in rheumatic disease was not supported by direct evidence.[637]

The mechanism by which pregnancy often suppresses the activity of rheumatoid arthritis remained unknown.[1235] The blood levels of 17-hydroxycorticosteroids, measured in 124 pregnant women, were shown to increase gradually during pregnancy, so that during the last trimester they averaged at least four times the levels in nonpregnant women of the same age. Maximal levels were attained just after delivery, with a rapid fall by the sixth postpartum day.[739] Although the physiologic skin hypersensitivity to colostrum disappears regularly during pregnancy, this effect was not duplicated in nonpregnant adults by the administration of corticotropin or cortisone.[2381]

Pathologic Characteristics

The widespread mesenchymal distribution of the pathologic lesions of rheumatoid arthritis was reiterated.[755] These lesions were regarded as pleomorphic and characterized by three cardinal features: (1) granulation tissue and subsequent overgrowth of fibrous tissue; (2) necrosis, starting with fibrinoid degeneration and occasionally passing on to liquefaction and cavitation; and (3) chronic inflammation with infiltration, predominantly of round-cells and variable numbers of plasma cells, histiocytes and polymorphonuclear cells. The predominating feature was determined to some extent by the site of the lesion. The resulting granulomatous lesion was considered nonspecific, but its associated presence in joints, subcutaneous tissue, muscle and elsewhere "is sufficiently constant to provide a fairly characteristic picture of the disease as a whole."[755]

Nodules. The typical morphology of the mature subcutaneous nodule of rheumatoid arthritis, with its central, avascular area of necrosis, was reviewed.[755, 1029] Studies of young subcutaneous nodules of rheumatoid arthritis revealed a predominance of vascular granulation tissue with necrosis and pali-

sades of radially arranged, elongated, mononuclear cells at its periphery. It was suggested that the process of necrosis progresses centrifugally in relation to the blood vessels. Discrete inflammatory and necrotizing alterations were found in the vessels of these nodules, similar to lesions described in the striated muscles and synovial membrane of the same patients. It was concluded that blood vessels "play a special role in the pathogenesis of the rheumatoid nodule," and that vascular lesions in the nodule may be a local manifestation of a generalized, rheumatoid arteritis.[1979] Ingenious chemical studies demonstrated that the fibrinoid of rheumatoid nodules contained very little hydroxyproline, leading to the conclusion that "if collagenous material is at all present in the fibrinoid of the subcutaneous nodule, the amounts are negligible."[2317]

Joints. Necrobiotic lesions indistinguishable from those of subcutaneous nodules were described in synovial tissues.[755] The cellular reaction of rheumatoid arthritis in the periarticular as well as the articular tissue was in the form of chronic round-cell infiltration; the most characteristic cellular reaction was in the synovial villi, where large accumulations of lymphocytes and plasma cells formed the so-called Allison-Ghormley foci. It was repeatedly emphasized that such morphologic alterations in articular tissues are not specific for rheumatoid arthritis.[755, 1879] Furthermore, it was shown that histologic alterations in the synovial tissue from different areas of a single rheumatoid joint may show remarkable variations, ranging from intense inflammation to well marked fibrosis. The necessity for caution in attributing to therapy changes which may occur spontaneously in the synovial tissues of rheumatoid arthritis was pointed out.[459] A new instrument for punch-biopsy of synovial membrane was described.[1671]

Bones. Pathologic changes in bone often occurred simultaneously with those of synovial membrane and included round-cell infiltration of the epiphyseal marrow, as well as fibrosis. The latter may be accompanied by bone resorption near the affected area, thereby explaining the radiologic evidence of marginal erosion and cyst formation. The appearance of the subchondral plate was such as to suggest penetration by granulation or by fibrous tissue into the marrow from the synovial pannus, passing through cartilage and bone and fanning out in the marrow spaces.[755] In one case, granulomatous rheumatoid nodules were demonstrated in bodies of vertebrae with resultant bone destruction.[89] Xanthogranulomatous lesions in bone and soft tissue adjacent to affected joints were demonstrated in two cases of rheumatoid arthritis.[785]

Neuromuscular System. The most prominent lesions in skeletal muscles of patients with rheumatoid arthritis were those of atrophy and degeneration. These features were not specific for rheumatoid arthritis, but were common to all patients with muscular atrophy of disuse.[2137] Determination of the chemical constituents of skeletal muscle revealed no changes characteristic of rheumatoid arthritis. In the presence of muscle atrophy in rheumatoid arthritis, degenerative joint disease and gout, the outstanding analytic changes from normal were decreases in the concentration of total protein, myosin and adenosine triphosphate. There was no evidence of collagen replacement of myosin in the course of atrophy.[186]

Of 57 cases of rheumatoid arthritis in which the striated muscle was studied in serial sections, acute and subacute inflammation of small, muscular arteries was found in five; these same alterations were observed in casual sections from an additional case. Control and comparative studies led to the conclusion that the lesion, although

not distinctive in its histology, is a characteristic manifestation of rheumatoid arthritis.[1980]

It was again agreed that the focal collections of round cells in peripheral nerves and skeletal muscles of patients with rheumatoid arthritis were not specific for this disease, although the incidence of these lesions was significantly higher in patients with rheumatoid arthritis or other rheumatic diseases than in patients with non-rheumatic diseases.[458] Their presence could not be correlated significantly with age, duration, stage or activity of the disease, with the source of the specimen in relation to affected joints, or with the hyperplasia of lymphoid tissues which may accompany the disease. The opinion was expressed that the specificity in rheumatoid arthritis of a connective tissue lesion, such as the lymphorrhage, may depend upon quantitative as well as qualitative considerations.[755]

Cardiovascular System. The discrepancy between the high incidence of rheumatic heart disease in pathologic studies of rheumatoid arthritis and its infrequency in clinical studies stimulated further study of the heart in rheumatoid arthritis. In a study of the pathologic material of 105 cases of rheumatoid arthritis (including 17 with ankylosing spondylitis), six demonstrated frank rheumatic heart disease (mitral stenosis, rheumatic valvulitis, and myocarditis with Aschoff bodies), an incidence of 5.7%; minimal rheumatic heart disease (minor sclerosis of valves accompanied by fibrosis of the leaflets, with formation of thick-walled blood vessels) was present in only one; calcareous stenosis of the aortic valve occurred in five, or 4.8%. The total incidence of rheumatic heart disease in this group of 105 patients with rheumatoid arthritis was 11.5%, whereas the corresponding incidence of rheumatic heart disease in a control group of 1,154 consecutive necropsies was only 5.7%. It was concluded that the coincidence in rheumatoid arthritis of heart disease which is indistinguishable from rheumatic heart disease is more than fortuitous.[1977]

Granulomatous inflammation of the heart, similar to that seen in rheumatoid subcutaneous nodules, was again reported in isolated cases.[89, 1977] Rheumatoid endocarditis and aortitis with aortic valvular incompetency were also described.[123, 1660] There was no proof that healed or minor rheumatoid lesions of the heart may lead to deformities indistinguishable from those of rheumatic heart disease.[1976] Healed, idiopathic pericarditis was seen in approximately one fourth of the cases of rheumatoid arthritis, an incidence 17 times as great as that observed in control necropsies. It was not possible to estimate how many had originated as granulomatous or fibrinous pericarditis. Nevertheless, the high frequency of healed pericarditis was regarded as evidence of another common cardiac manifestation of rheumatoid arthritis.[1977]

Diffuse arteritis emerged as another systemic manifestation of rheumatoid arthritis.[458, 1572, 1776, 1979, 1980, 2221] Usually affecting large arterioles or small arteries, the lesion was generally acute or subacute rather than chronic, and involved most prominently the adventitia.[1980] Many authors agreed that the arteritis of rheumatoid arthritis showed features which helped to differentiate it from other types of noninfectious arteritis, such as periarteritis nodosa and lupus erythematosus.[1776, 1980] Except for the comparatively small amount of both necrosis of collagen and intramural vascularization, the lesion most closely resembled the arteritis of rheumatic fever.

Other Visceral Lesions. The commonly described rheumatoid lesions of the eye included uveitis and scleromalacia perforans.[357] The latter was the result of

typical rheumatoid nodules in the sclerae.[28, 771, 2104] Severe inflammatory changes involving not only the ciliary processes but also the retina and adjacent structures were observed. In two such cases there was new bone formation in granulation tissue in the retina of one and in the lens of the other.[1660]

Polyserositis, resulting in widespread plastic adhesions between the peritoneal, pleural and pericardial surfaces, as well as effusion into these cavities, was recorded in one case of rheumatoid arthritis. There was nothing characteristic about the lesions except that these three serous cavities were involved together, a picture similar to previous observations in rheumatic fever as well as in rheumatoid arthritis.[1660] Lymph node biopsies in nine patients with generalized rheumatoid arthritis revealed histologic reactions which were neither uniform nor specific for rheumatoid arthritis. In some instances the lesions were similar to, but not identical with, those of giant follicular lymphadenopathy (Brill-Symmers disease), lymphosarcoma and Hodgkin's disease.[1505]

Biopsies of the liver were done in 13 patients with rheumatoid arthritis; seven of these revealed histopathology, including amyloidosis in two.[1326] In another series of biopsies on 17 patients with rheumatoid arthritis, abnormalities of the liver were found in only four. The alterations were neither specific nor striking, and consisted of slight-to-moderate fatty infiltration and evidence of healing of a degenerative process. There was no correlation between the anatomic findings and the results of liver function tests.[1507]

Laboratory Studies in Rheumatoid Arthritis

A review of procedures useful in the diagnosis and during therapy of rheumatoid arthritis served to underline the fact that available tests leave much to be desired, particularly with respect to specificity.[2230]

Hematologic Studies. Studies of over 200 patients with rheumatoid arthritis indicated that the anemia, the severity of which paralleled to some degree the activity of the disease, is normocytic and hypochromic, and that "undue hemolysis of not of importance."[1073, 1074] Results of blood volume studies yielded conflicting results. Some found that the plasma volume was usually normal, but in severe anemia the volume of erythrocytes was low, resulting in a reduction of total blood volume.[1073, 1074] From another study the conclusion was drawn that the anemia is due to hemodilution produced by an increase in plasma volume.[788] The sternal marrow was essentially normal, although there was evidence of minor disturbance in production of erythrocytes and hemoglobin.[1073, 1074] Bone marrow studies in another series of patients with rheumatoid arthritis revealed an increase in plasma cells, with concentrations varying from 1.8 to 6.3%.[934, 2230]

Serum iron was reduced, but iron transport and iron-binding capacity of the rheumatoid serum were not believed to be a factor in the anemia.[265, 1073, 1074] The serum copper level was elevated.[265] Oral iron-loading indicated that the absorption of iron in patients with rheumatoid arthritis may actually be better than normal. It was cautioned, however, that such an impression may require qualification, since the rate of clearance of iron from the serum was not measured, and may be slower than normal.[2084] Because of the similarity in structure of the enzyme catalase and hemoglobin, measurements of catalase in erythrocytes and plasma were made in anemic and non-anemic patients with rheumatoid arthritis, and in normal controls: there was no significant differential in concentration between the three groups of patients.[1072]

Lupus erythematosus (L-E) cells were described in patients with severe rheumatoid arthritis.[1572] They were also seen in rheumatoid patients during therapy with cortisone.[1944] [The status of the L-E cell in rheumatoid arthritis is confusing because of the varied methods employed in performing the test, and because there is not complete agreement as to the characteristics which identify the L-E cell. Many patients formerly considered to have classic rheumatoid arthritis are being reported to demonstrate the L-E phenomenon. Additional studies will be necessary to determine the significance of these observations.—Ed.]

Sedimentation Rate. Close correlation was observed between the rapidity of the sedimentation rate, the plasma fibrinogen concentration, and the severity of rheumatoid arthritis; exceptions were seen in the presence of markedly elevated serum globulins and of severe anemia.[665] Both sedimentation rates and concentration of plasma fibrinogen were reduced in most patients during therapy with corticotropin. In patients receiving such therapy, the Westergren method was believed to be more reliable than the Wintrobe method in the evaluation of activity of rheumatic disease.[783] The mean values by the Westergren method were found to increase with age. An upper limit of normal was about 20 mm. at the end of one hour for young adults and about 35 to 40 mm. per hour for elderly individuals.[2248] The influence of fibrinogen and globulin fractions on the sedimentation rate was demonstrated in a quantitative study, and the shortcomings of correction for anemia on the basis of the hematocrit were emphasized.[1455]

Serum Proteins. Electrophoretic studies of serum proteins in rheumatoid arthritis revealed a beta-globulin anomaly in the descending boundary pattern in 12 of 20 patients. No correlation with sheep-cell agglutinins was noted.[1730] In other studies, hyperglobulinemia and other nonspecific changes in serum protein concentrations were again observed.[948, 1326, 1344, 1832] Significant correlation of positive thymol turbidity reactions with positive streptococcus agglutination reactions was demonstrable, but without apparent practical application to diagnosis or prognosis.[1098] Other workers could show no correlation between gamma-globulin concentration and the antistreptolysin titer.[285]

Spinal Fluid. Whereas the abnormality in the serum protein of patients with rheumatoid arthritis was due to increases in the globulin fractions, variations in the spinal fluid total protein, albumin and globulin fractions occurred simultaneously and in the same direction. In a study of 23 cases of active, peripheral rheumatoid arthritis, high levels of spinal fluid protein correlated well with the high levels of the serum protein. However, it was not possible to relate the results to the clinical findings, and it was concluded that the estimation of the spinal fluid protein is of no clinical importance in rheumatoid arthritis.[1844]

Roentgenograms. The radiologic features of rheumatoid arthritis were investigated by a survey of routine films in 200 cases of the disease and by the application of a special enlargement technic. Most cases presented at least one radiologic abnormality within three to six months of onset. However, a few mild cases remained radiologically negative for two to three years. [Swelling of soft tissue was not included in this survey.—Ed.] Bony erosions and uniform reduction of joint space were the most frequent abnormalities, occurring in about 75% of the cases; osteoporosis was present in 64%. Either alteration of joint space or osteoporosis was the earliest abnormal feature. The joints most com-

monly affected were the metatarsophalangeal joints, especially the fifth. Since these joints were thought to provide the most accurate diagnostic information when there is also clinical evidence of their involvement, radiographs should be exposed for optimal viewing of this region rather than of the foot as a whole. After the feet, the hands were most productive of diagnostic information, with the second and third metacarpophalangeal joints affected most often. It was felt that the value of osteoporosis as a radiologic sign of rheumatoid arthritis has been over-emphasized. The lesser degrees of osteoporosis were difficult to evaluate, even with the use of controls; furthermore, the patterns of osteoporosis seen in rheumatoid arthritis are found in various other conditions.[667] Alterations visualized radiographically in the fatty content and muscular volume of the extremities of patients with rheumatoid arthritis could be correlated with the severity of the disease.[1043]

Serologic Tests. Agglutination by rheumatoid sera of sheep cells sensitized with antisheep hemolysin was the subject of further extensive study.[101, 976, 1862, 2077, 2078, 2079, 2175, 2232, 2266, 2267] Various modifications were proposed to increase the specificity and sensitivity of the test.[928] In general, the specificity decreased as the sensitivity increased.[100] Positive results ranged between 48%[2266] and 89%[2079] of the sera from rheumatoid patients. The test was positive in the joint fluid in 12 of 17 patients with rheumatoid arthritis. The titers correlated well with those obtained in serum of some patients, but in others there was striking discordance between values in joint fluid and serum.[2079] Positive tests among control series, which included patients with diseases other than rheumatoid arthritis as well as normal persons, varied between 1.6%[928] and approximately 20%;[2079] they were most common in patients with disseminated lupus erythematosus and other allied connective tissue diseases, exclusive of rheumatic fever. The test was often positive in patients with rheumatoid arthritis of one year's duration or less;[101, 1653, 2266] one positive reaction was recorded as early as five weeks after the onset of symptoms.[101] In at least one series of cases of rheumatoid arthritis, the incidence of positive tests was higher with increase in duration of the disease.[101] In another study, this variation with the duration of rheumatoid arthritis was not observed.[1653] Positive results were obtained also in patients whose arthritis was clinically inactive.[101] The test did not reflect clinical changes associated with treatment of the disease with gold, corticotropin or cortisone,[101, 1653] and remained negative in some patients despite severe and progressive disease.[1653] Negative agglutinations were usually obtained in patients with ankylosing spondylitis, rheumatoid arthritis associated with psoriasis, juvenile rheumatoid arthritis, gouty arthritis, degenerative joint disease and rheumatic fever.[101, 2079, 2232, 2266]

Studies of the mechanism of the test suggested that the factor responsible was not an antibody in the true sense of the word.[2080] The reaction was enhanced in the presence of normal animal sera[1652] and was obtained with cold precipitable substances from serum of patients with rheumatoid arthritis.[2081] [The specificity and sensitivity of this test have been considerably enhanced by the recent demonstration by Heller and associates and by Ziff and co-workers of an inhibitor of hemagglutination and by a method for its partial separation.—Ed.]

Other Tests. Elevation in the serum of nonglucosamine polysaccharides and hexosamines (the nonspecific alterations called "acute phase reactants") was described in patients with rheumatoid arthritis (juvenile), as well as in those with

rheumatic fever and other allied diseases.[1119, 1120] Shetlar and co-workers found such serum nonhexosamine polysaccharides increased consistently in rheumatoid arthritis, but not in degenerative joint disease. The finding was not specific for rheumatoid arthritis, and showed no good correlation with the sedimentation rate.[1902] With an ingenious adaptation of spectroscopic oximetry technics, it was possible to evaluate objectively the degree of involvement of rheumatoid joints by the degree of local anoxia.[547]

Etiology and Pathogenesis of Rheumatoid Arthritis

Factor of Infection. Efforts to transmit rheumatoid arthritis to human beings by the direct passage of rheumatoid synovial fluid were unsuccessful.[1277] The failure of homologous rheumatoid nodules to survive in transplant suggested that they are not the result of living agents.[122] Most observers,[200, 519] but not all,[400] agreed that the presence of focal infection in rheumatoid arthritis has no established significance. Of 37 rheumatoid patients who developed an acute infection, 24 showed a coincidental exacerbation of the arthritis.[1067] After detailed studies of the streptococcus agglutination reaction, Oker-Blom [1577, 1578, 1579] concluded that "the agglutination of living hemolytic streptococci by sera of patients with rheumatoid arthritis is caused by a non-specific factor (or factors) . . . and accordingly this agglutination cannot, without further evidence, be regarded as proof for the streptococcal etiology of rheumatoid arthritis." Four cases of arthritis, "clinically indistinguishable from rheumatoid arthritis," were the alleged result of chronic intestinal amebiasis.[1718] In another report, *Endamoeba histolytica* were found in the stools of 92 of 101 consecutive rheumatoid patients, thereby suggesting an etiologic relationship between amebiasis and rheumatoid arthritis.[1757] [This high incidence of intestinal amebiasis in rheumatoid arthritis is totally inconsistent with general experience.—Ed.]

Factor of Hypersensitivity. Pleuropneumonia-like organisms were regarded as possible antigens in a reaction of hypersensitivity which results in connective tissue disease. The severity of an exacerbation of rheumatoid arthritis following the administration of an antibiotic was stated to parallel the effectiveness in vitro of that antibiotic against L organisms. Such a reaction presumably represented the tissue response to an antigen released from the L organisms by the effect of the antibiotic; this reaction could be modified by administration of agents which interfere with hypersensitivity reactions.[284, 2243] [This hypothesis would gain more support if serologic reactions to pleuropneumonia-like organisms could be demonstrated in patients with rheumatoid arthritis.—Ed.]

Evidence of the existence of antibodies to extracts from diseased teeth led Dittmar to link focal infection to rheumatoid arthritis through a hypersensitivity mechanism.[527] Similar studies by Dietz were inconclusive.[519] A hypothesis on the "physiochemical pathogenesis of hypersensitivity states and collagenous disease" was based on the pharmacologic actions of acetylcholine and histamine, which are "insufficiently antagonized by enzyme-forming steroids from the adrenal cortex."[1066] [Experimental data are conspicuously absent.—Ed.] A discussion of the role of bacterial allergy in rheumatoid arthritis was equally unimpressive.[204]

Unlike the decreased serum complement titers in patients with disease known to be of allergic origin, the serum complement in rheumatoid arthritis was often elevated.[2167] The reaction to tuberculin was more feeble in adults with rheumatoid arthritis than in tuberculous patients or normal individuals. This suggested that patients with rheumatoid arthritis may have "a poor capacity to react allergically."[2203]

Inasmuch as cortisone and corticotropin have an inhibitory effect upon tuberculin hypersensitivity, the effects of other substances which inhibit experimental tuberculin hypersensitivity were studied in patients with rheumatoid arthritis. Neither the arthritis nor the patient's reactivity to purified protein derivative or tuberculin was influenced by these agents.[1323] These observations do not support a suggested analogy between experimental tuberculin hypersensitivity and the tissue reactions in rheumatoid arthritis. [Attempts to explain the action of adrenocortical steroids by inhibition of a postulated hypersensitivity mechanism are dealt with in the section on The Adrenals and Rheumatic Diseases.—Ed.]

Factor of Altered Metabolism. Significant increase was shown in urinary excretion and plasma values of certain amino acids in patients with rheumatoid arthritis during treatment with corticotropin. The changes were greater than those observed in normal adults and were regarded as indicative of "changes in intrinsic protein metabolism."[235] In another study, a deficiency of extrahepatic glycine available for hippurate synthesis was presumably demonstrated. Because of the uniquely high concentration of glycine in collagen, it was suggested that a failure of supply of glycine could lead to impairment in production of normal collagen, or to the formation of abnormal collagen of poor quality.[1266] Elsewhere, it was pointed out that collagen, once laid down in growth, may remain in a state of metabolic inertia for long periods; therefore, rapidly developing disorders of collagenous tissue, such as rheumatoid arthritis, are unlikely to result from faulty collagen synthesis, but rather from disintegration.[1125] Alteration of the metabolism of hyaluronic acid in both rheumatic fever and rheumatoid arthritis was believed responsible for a delayed reconstitution of the dermal barrier following the injection of hyaluronidase.[820]

A significant or characteristic abnormality in the metabolism of creatine was not demonstrated in patients with rheumatoid arthritis or with degenerative joint disease.[497] Inasmuch as pitressin inhibits the activity of adenosinetriphosphatase, it was believed that the favorable short-term effects of pitressin on patients with rheumatoid arthritis lend support to the contention that "heightened adenosin triphosphatase activity of tissue underlies the rheumatoid process."[920] Quantitative alterations of the levels of glutathione in erythrocytes were not attributable to rheumatoid arthritis.[2206]

Factor of Endocrine Imbalance. It was the opinion of at least one observer that a disturbance involving the pituitary or adrenals, or affecting the metabolism of their hormones, may be an important factor either in the development of rheumatoid arthritis, or in a lack of protection against its development.[932] Distinctive cytologic alterations of the type associated with adrenal dysfunction were described in the pituitary glands of patients with rheumatoid arthritis.[1624] [Efforts to confirm this work should be most valuable.—Ed.]

In further studies of the 17-ketosteroid excretion in series of 80 patients[271] and of 55 patients[2230] with rheumatoid arthritis, most of the values fell within the normal range, and the distribution was independent of the stage of the disease. Corresponding findings were found on examination of "glucocorticoid" excretion.[271] The blood level of 17-hydroxycorticoids in a few patients with rheumatoid arthritis were in the same range as in normal subjects.[1527] In 10 patients with rheumatoid arthritis, the ACTH activity of the plasma as determined by bio-assay was lower than in normals.[345] Only seven of 51 patients with this disease failed to show a normal eosinopenic response to epinephrine.[1608] However, from a preliminary study of steroid hormone

metabolites in five patients with rheumatoid arthritis, Dobriner found evidence of both a quantitative and a qualitative abnormality, suggesting a basic imbalance in steroid production and/or metabolism. Not only was the excretion of the usual steroid metabolites at a consistently low normal level, but also four of the five subjects excreted an abnormal steroid, 17-hydroxy-pregnenolone. The steroid imbalance was lessened but not eliminated following corticotropin administration.[533] More recently, new technics have also suggested that there are significant changes in the pattern of urinary steroid excretion in patients with rheumatoid arthritis.[1133, 1557] [It is not yet possible to evaluate the etiologic significance of these interesting observations.—Ed.]

It was more generally felt that rheumatoid arthritis probably is not the result of adrenocortical insufficiency or any other disorder of endocrines.[122, 271, 566, 1125] Metabolic alterations, such as negative nitrogen, calcium and phosphorus balance, could be corrected without influencing the disease.[122] The association of rheumatoid arthritis with Addison's disease or other disease of the adrenals was rare.[338, 1298] Three patients who had developed rheumatoid arthritis two, five and 13 years after the onset of panhypopituitarism were reported.[1856, 2065] Rheumatic disease was not found in patients with the adrenogenital syndrome, a condition resulting from inadequate production of carbohydrate-active steroid.[122] Although the clinical effects of cortisone and corticotropin are profound, it was felt that rheumatoid arthritis is not the result of temporary or long-standing deficiency of cortisone.[122] Certain important features of rheumatoid disease were not altered by the administration of cortisone or corticotropin, including the fibrinoid core of rheumatoid nodules, the atrophy of connective tissue, and the positive agglutination reaction. The dramatic clinical effects of these hormones were attributed to their suppression of the body's reaction to the essential rheumatoid lesion.[1125]

Since it had been shown that plasma levels of beta-glucuronidase increase during pregnancy in nonarthritic women, it was disappointing to demonstrate no significant deviation from normal in patients with rheumatoid arthritis.[116] The possible endocrine role of the spleen in rheumatoid arthritis was the subject of further but inconclusive study.[832]

Factor of Autonomic Imbalance. It was demonstrated that the cutaneous blood flow was decreased in the extremities of patients with rheumatoid arthritis, while the "deep blood flow" of affected limbs was increased, as was the cardiac output.[1124, 1125] Tests of thermal response showed a poor degree of vasodilatation in patients with rheumatoid arthritis.[705, 2285] Improvement in vasomotor activity followed the administration of corticotropin;[135, 1524] the accelerated response in other rheumatoid limbs to a thermal stimulus in one suggested that the effect of the hormone is neurovascular, via the thermoregulatory mechanism.[135] Reflex neurogenic factors were regarded as significant in the spread of rheumatoid inflammation.[1136] Administration of a sympathicolytic drug (methane sulfate of hydrogenated ergotamine) to patients with rheumatoid arthritis occasionally ameliorated symptoms,[2072] while the use of a parasympathicolytic drug (atropine) was often followed by an exacerbation of the disease.[1069] Studies of intra-articular temperatures indicated that neither vasoconstricting nor vasodilating drugs have any significant influence on the synovial circulation in rheumatoid arthritis.[998]

Psychogenic Factors. Psychoanalysis of eight patients with major emotional problems in addition to their rheumatoid arthritis revealed grossly abnormal personality traits which, while not specific for rheumatoid arthritis, were similar to those of a large number of unselected rheumatoid patients previously interviewed over sev-

eral years. Despite outwardly normal social adjustment, these subjects manifested emotional immaturity, insecurity and, at times, depression of varying intensity, not only in the pre-arthritic stage but also during remission of joint symptoms as well. Outward expression of emotion was difficult. Such patients employed the common psychologic defense of attempting to deny or negate their feelings of helplessness. All were sensitive to any loss of emotional support; both the onset of rheumatoid arthritis and its subsequent exacerbations were seemingly related to emotional events which implied loss of security, resulting in disruption of unstable homeostatic mechanisms.[1837] [To date, the crucial experiment showing the influence of the central nervous system on the inflammatory lesion of rheumatoid arthritis has not been done.—Ed.]

Factor of Heredity. Evidence is accumulating that rheumatoid arthritis, as well as other rheumatic diseases, occurs in those persons who have a genetically predisposed constitution or susceptibility.[1962] In 100 patients with rheumatoid arthritis, the familial incidence of rheumatoid arthritis and rheumatic fever was 5.3%, as against a familial incidence of 2.3% in 100 controls.[115] Another study was based on the pedigrees of 224 patients with rheumatoid arthritis, including 1,677 persons, and compared with the pedigrees of 488 controls, including 2,759 persons. Of the relatives of the rheumatoid patients, 3.1% of the total had rheumatoid arthritis, compared to 0.58% of all relatives in the control group. These figures were felt to indicate a hereditary factor in rheumatoid arthritis, and the collective data (after calculations and corrections peculiar to the field of genetics) suggested that rheumatoid arthritis may be an autosomal dominant characteristic, with about 50% penetrance. It was thus estimated, on the basis of the 0.58% familial incidence in the control group, that 1.16% of the population have the genetic constitution for the disease.[2011] [To date, this genetic constitution has not been clearly defined.—Ed.]

Conclusions Regarding Etiology. Neither the inciting agent of rheumatoid arthritis nor its pathogenic mechanism is known.[122] However, new investigative approaches by histochemists, chemists and biophysicists promise to yield valuable new information which may throw light on these problems.

Relationship Between Rheumatoid Arthritis and Other Diseases

Other Connective Tissue Diseases. The pathologic and clinical similarities between rheumatoid arthritis and rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis and scleroderma are well known. There appeared to be a slight predisposition for rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa and chronic peptic ulcer to coexist with rheumatoid arthritis.[1976] Peripheral rheumatoid arthritis was not once observed in a follow-up study of 137 unselected veterans who had had rheumatic fever during World War II.[612] A syndrome occurring in elderly patients, with manifestations resembling the prodromal stage of rheumatoid arthritis, was regarded as more closely related to rheumatoid arthritis than to other "collagen diseases." The outstanding features were fever, muscle aching and anemia; the joints were not necessarily involved.[93]

Other Diseases. A primary generalized form of chronic arthritis, occurring predominantly in middle-aged women, was believed to combine some features of both rheumatoid arthritis and osteoarthritis. It was characterized by progressive symmetric inflammation of larger joints in sequence, with rapid progression of cartilage and bone changes.[2192] [We would regard such cases as a variant of rheumatoid arthritis.—Ed.] Preëxisting rheumatoid arthritis was noted in two of four cases of acrosclerosis.[1714] There was no increase in the incidence of rheumatoid arthritis among patients

with parkinsonism.[2182] A patient with coexisting rheumatoid arthritis and sarcoidosis was reported.[489] Another patient with rheumatoid arthritis gave a past history which was compatible with Reiter's syndrome.[1302] The opinion was expressed that chronic arthritis following gonococcal or nonspecific urethritis is a distinctive entity from which rheumatoid arthritis can be distinguished.[670] [This is at variance with commonly expressed opinion.—Ed.] A case of coexisting rheumatoid arthritis and perifolliculitis capitis abscedens et suffodiens ("a rare form of suppurative and cicatrizing disease of the scalp") was reported.[2199]

Juvenile Rheumatoid Arthritis

Juvenile rheumatoid arthritis was more frequent than was formerly believed, and accounted for about 4% of all rheumatoid patients.[105, 304] The disease occurred most often at the age of three years and again between eight to 11 years of age, with a ratio of two females affected to one male. A family history of rheumatic disease was present in 20 to 30%. Onset of the arthritis followed an upper respiratory infection in 45%. One type was limited mainly to joint involvement, while the other type was associated with severe constitutional manifestations, such as high fever, lymphadenopathy, anemia, splenomegaly, pleuritis, pericarditis, amyloidosis, severe muscle wasting and other visceral lesions. Joint involvement resembled the adult form except that the cervical spine was commonly affected. Duration of the active disease varied from a few months to periods as long as 10 to 40 years of continuous or recurrent activity. During the first 10 years, continuous activity or recurrences were the rule, and the disease did not terminate at puberty. Differential diagnosis was often difficult; the disease was most often confused with rheumatic fever, less commonly with tuberculosis, leukemia, traumatic or infectious arthritis, and nonspecific synovitis.[105] The dominant feature at time of onset in 19 patients was high fever, and at times a macular rash. While at that time there was typically a leukocytosis in the region of 17,000 to 30,000, with pronounced neutrophilia, no evidence was found that this disease can ultimately be transformed into leukemia.[1847] Radiologic changes and frequent growth complications, such as short, stubby fingers, receding jaw, shortened, unequal or deformed extremities, fusion and ankylosis of the cervical spine, and dwarfism, were reviewed.[105, 1462] Amyloidosis was a fatal complication in five patients.[62, 105, 1062]

Barkin summarized long-term observations on 51 patients cared for in a chronic disease hospital. Heart involvement occurred in 16 of the 51 patients at some time during their illness, and five developed rheumatic valvular disease. He considered the prognosis of juvenile rheumatoid arthritis to be serious, since 20% of the patients died, 39% were incapacitated, and only 41% had good functional recovery. Causes of death were pulmonary disease, amyloid disease, and aortic valvulitis with congestive failure.[105] [The apparent prognosis will depend on the type of juvenile rheumatoid arthritis being cared for by the institution or individual reporting. If this is a hospital devoted to severely afflicted patients with rheumatoid arthritis, the mortality is high. The outlook is much better in the type of disease usually seen in a general hospital or in practice.—Ed.]

Treatment. The availability of cortisone or corticotropin therapy improved the prognosis in this disease, especially in the severe systemic type of disease when invalidism or death threatened.[304, 1201, 2170, 2187] Prolonged treatment with

cortisone produced improvement in all patients reported, with continued remission in some after hormone therapy was discontinued. However, radiologic evidence of disease progression occurred in several patients who experienced clinical improvement.[304] [The principles of treatment for rheumatoid arthritis in adults apply equally to this disease in children.—Ed.]

Treatment of Rheumatoid Arthritis

It is important to use a well-rounded treatment program carefully adapted to the need of each individual patient, rather than to rely on any single method of treatment.[408, 438, 703, 1775] Practical objectives of management were defined as (1) relief of discomfort; (2) maintenance of good joint function; (3) prevention of deformities; (4) maintenance of good nutrition; (5) correction or control of complications; (6) arrest of the rheumatoid process; (7) correction of deformities if developed, and (8) rehabilitation of the crippled.[703] Admittedly, the most difficult of these objectives to achieve is arrest of the activity of the rheumatoid process. "In recent years, a better understanding of the disease . . . and the addition of several new therapeutic agents has made treatment more rewarding and has awakened an intelligent interest on the part of many physicians." [703]

Problem of Evaluating Treatment. Evaluation of the treatment of rheumatoid arthritis is complicated by lack of knowledge of its pathogenesis and of those factors responsible for its variable course.[1706] In the critical appraisal of therapeutic methods or agents in this disease, the term "improvement" embraced a variety of changes in its manifestations ranging from remissions of articular or systemic signs of inflammation to purely functional gains.[867] Therapeutic evaluation has continued to be handicapped by the lack of uniform methods of measurement, the inadequacy of objective tests, the absence of standardization of cases, and the failure to use placebos.[120, 927, 1009, 1335, 1779] Moreover, general agreement on a definition of a remission has not been achieved.[414]

An important advance in the study of rheumatoid arthritis in recent years has been the application of a more rigid clinical discipline in the assessment of therapy.[567] Measures were proposed to permit more critical assessment of therapeutic measures by minimizing psychologic factors,[862] by appraising the "experimental error" of such trials and applying better methods of statistical control,[138] and by determining the frequency of spontaneous remissions.[87]

Methods for objective measurement included automatic still and motion photography for assessment of joint function,[1335] and thermocouple measurements to record changes in intra-articular temperature in inflamed joints.[994] [Application of the objective classification and therapeutic criteria adopted by the American Rheumatism Association (Tenth Rheumatism Review) has produced a variety of results with specific therapeutic agents. Misinterpretation or misapplication could be construed in some reports where such criteria, designed solely for use in rheumatoid arthritis, have actually been applied to rheumatoid spondylitis, degenerative joint disease and certain collagen diseases. Nevertheless, despite definite shortcomings, these criteria remain the best available at the present time to record objectively the stage of disease progression, the classification of functional impairment, and the grading of response to therapy.—Ed.]

Rest and Motion

Some degree of physical rest was advocated.[215, 216, 565, 567, 1702, 1775, 1949, 1992] Complete bed-rest at the beginning of therapy was advised, with proper attention to prevention of deformities.[1309, 1310] However, in the treatment of ordinary cases, 10 hours of rest at night and one or two hours during the day were considered adequate.[216] The importance of measures for maintaining the general level of physical and cardiovascular efficiency was emphasized.[565] Local rest of the involved joint during the early days of therapy was considered important in ameliorating local inflammatory processes.[1440] [No experimental data were presented.—Ed.]

Analgesics

Salicylates and Related Agents. Salicylates continued to be the most popular analgesic agents.[216, 703, 1309, 1310, 1702, 1775, 1928, 1992] The most common cause of their failure was improper spacing of doses and inadequate total daily dosage.[703] The combination of calcium succinate and aspirin was found to have no advantage over aspirin alone.[445, 2129] The combination of sodium salicylate and para-aminobenzoic acid resulted in higher blood salicylate levels, but otherwise was not superior to sodium salicylate alone.[992] The combination of calcium pantothenate with sodium salicylate or aspirin was thought to be better tolerated than sodium salicylate alone in 20 of 28 patients.[2145] Sodium gentisate was found to have approximately the same potency as aspirin when administered in proper doses.[118]

Phenylbutazone. Phenylbutazone (3,5-dioxo-1,2-diphenyl-4-n butylpyrazolidine; "Butazolidin") was first synthesized in 1948 to be used as a solvent for the intramuscular administration of aminopyrine. Preparations of aminopyrine in phenylbutazone, trade-marked Igrapyrine (Europe) and Butapyrin (U.S.A.), were found to have analgesic and antipyretic properties in arthritis and related diseases. It was learned that the solvent alone (phenylbutazone) had similar therapeutic properties.[1948] In 1951, clinical trials with an oral preparation of phenylbutazone were initiated in patients with rheumatoid arthritis and resulted in substantial degrees of improvement in a large percentage of cases.[314, 462, 465, 466, 482, 691, 788, 823, 1139, 1159, 1222, 1223, 1224, 1227, 1333, 1387, 1614, 1814, 1948, 1971, 2031, 2039]

Pharmacology. Determination of plasma levels revealed rapid absorption of phenylbutazone from the gastrointestinal tract, with peak plasma concentrations occurring approximately two hours after a single oral dose, and six to 10 hours after intramuscular administration. Repeated daily doses of 800 mg. per day resulted in stable plasma levels of 90 to 130 mg. per liter at the end of three to four days. Approximately 98% of the drug was found in the plasma, bound to plasma protein. In a patient with rheumatoid arthritis receiving 800 mg. per day, the synovial fluid contained 80 mg. per liter at the time the level in plasma was 145 mg. per liter. Approximately 20% of the drug disappeared from the plasma daily, and seven to 10 days were required for complete disappearance. It was excreted in the urine with almost complete transformation of the drug to three metabolites.[309a] Less than 10% of the daily dose was recovered in the urine.[2007] Prolonged administration to a dog in doses of 250 mg. per kilogram per day resulted in weight loss and anemia, and death in the twelfth week. Feeding studies in rats using concentrations of 0.5% in drinking water resulted in decreased food intake and retarded growth during the 90-day period of observation.[925] A human subject inadvertently ingested 4.0 gm. without toxic effects.[314]

Physiologic Effects. Sodium, chloride and water retention were observed during the administration of phenylbutazone.[826, 2249] Potassium balance was not altered, and glomerular filtration rate was unchanged.[2249] It was suggested that the effect of phenylbutazone on salt balance was mediated through a renal tubular mechanism.[2249] No antidiuretic hormone-like effect was observed,[826] and adrenocorticotropic effects could not be demonstrated.[482] Radioactive iodine uptake was diminished by phenylbutazone.[828, 1863]

Nature of Clinical Response in Rheumatoid Arthritis. Improvement in both subjective and objective manifestations of rheumatoid arthritis was observed during the administration of phenylbutazone.[314, 1222, 1223, 1224, 1227, 1948, 2031, 2039] Convincing improvement was demonstrated in controlled studies using placebos.[482, 691] The favorable effects of phenylbutazone included relief of pain, increase in joint motion, improved strength and, occasionally, diminished joint swelling.[2039] Major improvement (grades I and II remissions according to therapeutic criteria established by the American Rheumatism Association) resulted in 23% of 117 patients,[2031] 59% of 163 patients,[1227] and 92.5% of 40 patients.[314] Not all investigators were convinced that significant objective improvement was achieved; many considered its effect to be essentially analgesic.[1159, 1387, 1614]

While most reports dealt with observations over a period of only a few weeks or months, improvement for as long as nine months was seen in some patients.[1159] Of a series of 164 patients with rheumatoid arthritis, 70% improved subjectively during the first month, but only half of this group had maintained their improvement at the end of six months.[691] Maintenance of improvement required the continuous administration of the drug.[930, 1222, 1227] Consistent decreases in the erythrocyte sedimentation rate were not observed during phenylbutazone therapy.[482, 691, 1159] However, in some instances reductions in the sedimentation rate were considered significant.[462, 465] [The precise nature of the effects of phenylbutazone on the manifestations of rheumatoid arthritis has not been determined. Although objective improvement has been noted during the administration of this drug, specific antirheumatic effects have not been proved.—Ed.]

Dosage of Phenylbutazone. Therapeutic effectiveness was found to be correlated with plasma levels.[1159] For initial control of symptoms, plasma concentrations of 80 to 111 mg. per liter were considered necessary. Such levels were achieved by daily doses of 800 mg. per day, later tapered to doses of 200 mg. per day.[466] Kuzell considered the initial optimal dose to be 600 to 800 mg. per day,[1227] but Steinbrocker considered doses of 400 mg. per day to be as effective as 800 mg. per day in most patients.[2031] [In view of the toxic effects,[2028] lower doses of 200 to 400 mg. per day or less have been more generally adopted.—Ed.]

Toxic Reactions to Phenylbutazone. The incidence of toxic reactions was high.[314, 482, 691, 788, 816a, 1139, 1223, 1227, 1267, 1440a, 1814, 2031, 2039] In the largest series—800 patients—40% developed some evidence of toxicity; this was severe enough to require discontinuation of the drug in 15% of the 800.[1227] Review of the literature prior to June, 1953, yielded an average of 22% of 1,526 patients who experienced toxic reactions.[1267] Eleven deaths attributed to this drug were reported in some detail;[161, 179, 482, 520, 627, 1267, 1440a, 1526, 1689, 2024] two others were briefly noted.[1441] [Most of these reports included patients with a variety of disorders as well as those with rheumatoid arthritis. Since the general manifestations and incidence of toxicity are much the same in all patients receiving phenylbutazone,

no attempt has been made in this review to separate the reports according to the disease being treated.—Ed.]

Edema was attributable to sodium retention.[826] It occurred in 14% of patients in two large series,[691, 1227] and was noted by most workers. This effect presumably was responsible for occasional cases of hypertension,[1227] pulmonary edema[314] and congestive heart failure.[1227, 2031, 2039] Other cardiac complications included tachycardia,[466] arrhythmias[1227] and myocardial infarction.[2031]

A drug rash occurred in 5% or more of cases.[314, 466, 482, 757, 788, 816a, 823, 837, 1227, 1274, 2031, 2039] Severe systemic hypersensitivity reactions were reported;[351, 660, 1274] one such reaction was fatal.[1526] Dryness of the mouth and throat and aphthous stomatitis were not infrequently encountered.[466, 1227, 1525, 2031]

Gastrointestinal symptoms, most commonly nausea, diarrhea or constipation, occurred in 15% or more of patients.[466, 691, 788, 1139, 1227, 1525, 2031, 2039] Many instances of activation or development of peptic ulcer were reported.[462, 520, 823, 1199, 1614, 1701, 2039] Ulcer activation occurred in 1% of 800 patients, and 4% had epigastric pain.[1227] Gastrointestinal hemorrhage[462, 816a, 1199, 1226, 1227, 2039] and perforation[161, 179, 1906] occurred, and contributed to a fatal outcome in four patients, two of whom also had agranulocytosis.[161, 179, 520, 1441] Isolated cases of jaundice were also reported.[314, 1227, 1689, 2031]

Agranulocytosis was held responsible for seven deaths[161, 179, 520, 627, 1141, 1689, 2024] and occurred in at least 20 additional patients who recovered following discontinuation of the drug and the use of antibiotics.[177, 259, 969, 1145, 1161, 1227, 1267, 1525, 1689, 2049, 2233] Fatal aplastic anemia,[1267] severe hemolytic anemia[1139] and simple anemia,[314, 1227, 2039] as well as thrombocytopenia[1227, 2039] and nonthrombocytopenic purpura,[482, 1227] were noted. Some expressed the opinion that the use of small doses and frequent blood counts would minimize the dangers of bone marrow depression.[2060] But Kersley and Mandel observed agranulocytosis with depression of all marrow elements in a patient who received the drug for 17 days only at a dose never exceeding 400 mg. per day. They felt that routine white cell counts were useless, and that warning the patient to report malaise, fever and sore throat was a more important precaution.[1145]

Both central nervous stimulation and lethargy were reported,[1139, 1227] as well as psychosis[1227] and paresthesias.[466] One death following convulsions during administration of phenylbutazone was not adequately explained by clinical or autopsy findings.[482]

Edema complicating phenylbutazone therapy was controlled by mercurial diuretics[1814, 2031, 2249] or dietary sodium restriction.[482, 1227, 2031, 2039] Kuzell, however, found mercurial diuretics ineffective.[1227] The incidence of adverse effects was related to dosage levels.[1139, 1227] Toxic reactions were more frequent in females.[1227] Age seemed to be a factor in one clinical study[1139] but not in another.[1227]

The serious toxic potentialities of phenylbutazone posed a real problem regarding its use.[51] "Although the patient may often be prepared to take any risk for relief of symptoms, his physician usually is not."[904] In a symposium of the Empire Rheumatism Council it was concluded that, although antirheumatic action is hard to define, the action of phenylbutazone in this regard has not been convincingly established and there has been no suggestion of a curative action. "In these circumstances phenylbutazone should not be used merely as an alternative analgesic in rheumatism. Careful selection of patients and close

attention to signs of toxicity are now rightly demanded."[609] Recommendations to minimize dangers of toxicity included (1) restriction of its use to patients in whom less toxic drugs fail to give adequate relief; (2) avoidance of its use in patients with a history of peptic ulcer or allergy, and in the older age group; (3) keeping the total daily dose as low as possible, and (4) stopping the drug if no improvement is noted in five to seven days.[1971] [Most of us would agree with these recommendations, and regard phenylbutazone as a potentially dangerous drug unless precautions are taken. Even with precautions, it must be appreciated that serious depression of bone marrow elements may occur in an unpredictable manner. Some of us feel that the serious potential toxicity of phenylbutazone outweighs its inconsistent and unpredictable beneficial effect in rheumatoid arthritis, and rarely use it in this disease. Others feel that final judgment as to whether the possible benefit justifies the risk must be reserved until the influence of this drug on the course of rheumatoid arthritis is determined by additional long-term, controlled studies.—Ed.]

Cortisone, Hydrocortisone and Corticotropin in Rheumatoid Arthritis

Considerable experience accrued reaffirming the favorable effects of cortisone and corticotropin on the clinical manifestation of rheumatoid arthritis.[73, 176, 189, 215, 216, 219, 222, 223, 233, 271, 290, 301, 367, 408, 430, 432, 493, 567, 607, 657, 672, 692, 699, 702, 704, 751, 804, 812, 931, 932, 933, 982, 994, 1010, 1016, 1047, 1170, 1171, 1172, 1201, 1221, 1273, 1363, 1379, 1417, 1485, 1514, 1528, 1539, 1540, 1541, 1554, 1571, 1670, 1684, 1685, 1695, 1702, 1703, 1706, 1724, 1770, 1775, 1804, 1856, 1970, 1992, 1994, 2030, 2032, 2033, 2104, 2128, 2150, 2187, 2189, 2191, 2216, 2231, 2234, 2235, 2268, 2282] Moreover, previous observations of the antirheumatic properties of hydrocortisone were corroborated in more extensive clinical trials.[218, 220, 221, 224, 1634] [Reports concerning therapeutic results with these agents are too numerous to summarize. The nature of the response is now well known. Difference in degrees of response and total results have depended on many variables, such as severity of the disease, duration and dose of ACTH or steroids, adjunctive therapy, psychologic factors and therapeutic objectives. More recent observations have revealed potent antirheumatic effects of other steroids, namely, 9-alpha-fluorohydrocortisone, prednisone and prednisolone.—Ed.]

Nature of Clinical Response. The degree of responsiveness to standard doses of cortisone and corticotropin was found to vary.[1129] Better results were observed in less severe cases.[223] Totally unresponsive cases were observed, even with high doses of corticotropin or cortisone.[1129, 1147, 1695] Subjective and/or functional improvement was found to be a more significant feature of the response to adrenal hormone therapy than was objective improvement.[367] Symptomatic improvement was noted in 99 of 100 patients observed at the Mayo Clinic.[2191] When the objective criteria of improvement recommended by the American Rheumatism Association were applied during initial phases of therapy in 72 patients, Steinbrocker observed that 4% had grade I response, 40% grade II, 54% grade III, and 2% grade IV. During maintenance therapy (30 to 340 days), 5% had a grade I response, 27% grade II, 51% grade III, and 17% grade IV.[2030, 2033]

Relapse within 60 days after cessation of therapy was the rule, indicating that hormone therapy did not influence the ultimate course of the disease.[223, 301, 367, 699, 704] Specific effects observed during corticosteroid or corticotropin administration included amelioration of fever, joint swelling, flexion contractures, and enlarged lymph nodes,[931] reduction of joint temperature,[994] regression of

subcutaneous and scleral nodules,[73, 157, 301, 649, 931, 1029, 1514, 1555, 2104] improvement of iridocyclitis,[367, 979, 1514] disappearance of signs of pericarditis,[367] return of menses,[751] and increase in work capacity.[751] The systemic manifestations of juvenile rheumatoid arthritis were reduced.[2282] In general, long-standing deformities and flexion contractures were not benefited.[301]

Satisfactory long-term results were not achieved in all cases. Of 76 patients studied by Freyberg, 60 were able to continue therapy for six to 15 months; of these, 48 were classed as exhibiting satisfactory improvement.[704] Treatment failures were more common in patients with severe disease; such patients required larger dosages, with a resulting increased incidence of adverse hormonal effects.[223] Serial x-rays demonstrated progression of joint destruction during periods when the clinical manifestations were well suppressed by hormone administration.[367, 1695, 2235] [Roentgenographic evidence of progression in spite of apparent clinical improvement is not uncommon under other forms of treatment, and even during "spontaneous remissions." Such observations suggest that corticosteroid therapy, like other forms of treatment, is limited in its ability to alter the fundamental pathologic process in rheumatoid arthritis.—Ed.]

Cortisone and corticotropin facilitated the correction of deformities by physical or orthopedic measures.[189, 367, 1379, 1670, 1706, 1970, 2030] Following orthopedic procedures, postoperative pain was lessened and convalescence was shortened.[672]

Physiologic Effects. The administration of corticotropin resulted in changes in the distribution of extracellular and intracellular fluid and electrolytes which varied from patient to patient;[500, 716] similar variation was seen in normal subjects.[1197] Corticotropin increased peripheral blood flow,[135] although the effect was not uniform.[1124] Prompt reduction of intra-articular temperature was noted after the administration of ACTH or cortisone.[994] The effects of adrenal hormones on the electro-encephalogram were variable; improvement of previously existing abnormalities was noted in some cases of rheumatoid arthritis.[1655] [Other physiologic and biochemical effects are summarized in the section on "The Adrenals and Rheumatic Diseases."—Ed.]

Effects on Synovial Fluid. The synovial fluid abnormalities characteristic of rheumatoid arthritis were often diminished or reversed; the total leukocyte and polymorphonuclear cell count decreased, and the relative viscosity increased.[367, 751, 994] The increase in relative viscosity, sometimes to a value far above that seen in normal synovial fluid, suggested either a retardation of enzymatic degradation or an enhancement of enzymatic synthesis of synovial mucin.[751] Cortisone added in vitro had no effect on the viscosity of synovial fluids.[532]

Effects on Laboratory Tests. The erythrocyte sedimentation rate was found to have definite limitations as an index of the clinical effectiveness of corticotropin and corticosteroid therapy.[91, 432, 2168] The Westergren method of determination was preferred to the Wintrobe method as showing a better correlation with the clinical course during administration of these hormones.[783] Observed changes in the sedimentation rate were correlated with changes in the plasma fibrinogen levels.[865]

Abnormalities of the serum protein pattern, as determined by electrophoresis [167, 751, 948, 1582] and by polyfractionation technics,[591] showed definite reversion toward restoration of a more nearly normal pattern. An increase in albumin and decreases in the elevated values for fibrinogen, alpha$_1$ and alpha$_2$ globulins and gamma globulin were observed during treatment with cortisone or corticotropin. Such changes were seen in other diseases treated with these agents;[2274] some found that in rheumatoid arthritis the reversion to normal was not constant, and was not correlated with clinical improvement.[1442] The changes in plasma protein constituents were influenced by

changes in blood volume, and "may represent, at least in part, metabolic alterations induced by therapy but unrelated to improvement in the disease." [1062]

Preëxisting high serum complement titers decreased in six patients with rheumatoid arthritis during corticotropin therapy; abrupt increases followed cessation of treatment.[2167] No changes were observed in the titers of the streptococcus agglutination reaction or sensitized sheep cell reaction during hormone therapy.[167, 301, 432] Antistaphylolysin and antistreptolysin titers were decreased in one study [1596] but did not change in others.[301, 432] Levels of serum hyaluronidase inhibitor decreased rapidly to subnormal values in two children treated with corticotropin,[8] but other investigators observed no such effect.[1263a] Elevated serum polysaccharides were observed to return slowly to normal during therapy.[8] A decrease in the rate of destruction of heparin was also observed.[346]

Hematopoietic Effects. The administration of cortisone or corticotropin to patients with rheumatoid arthritis resulted in increases of the red blood count, hemoglobin and hematocrit in many, but not in all cases. Slight reticulocytosis usually resulted. Interpretation of changes in hemoglobin and hematocrit values was complicated by changes due to hemodilution, particularly in studies with corticotropin.[578, 650, 2084] Bone marrow studies during corticosteroid therapy showed erythroid hyperplasia and polymorphonuclear leukocytosis with greater maturity of the granulocytes.[167, 578, 650, 791, 1596] Mononuclear cells and lymphocytes were decreased.[578, 650] Most observers noted a decrease in plasma cells in the marrow,[167, 432, 791, 1596] but in one study plasma cells were not observed to be influenced by these hormones.[578] Plasma iron concentrations were elevated by adrenal hormone therapy in four of seven patients with abnormally low pretreatment values.[578] It was concluded that the favorable effect of cortisone or corticotropin on the anemia of rheumatoid arthritis resulted from suppression of the disease process rather than from direct hematopoietic stimulation.[650]

Effects on the Pathology of Rheumatoid Arthritis. Serial studies of synovial tissue during treatment with cortisone or corticotropin revealed various degrees of suppression of the inflammatory process.[367, 751, 1554, 1555, 1695] Microscopic examination of synovial biopsy material showed absence of edema, dense interstitial fibrosis, and decrease in perivascular lymphocytic infiltrates, but persistence of focal synovial degeneration.[751] Cruickshank [459] warned against attributing biopsy changes to corticosteroid therapy, since he observed major variations in the degree of inflammation and fibrosis in blocks taken from the adjacent sections of joints in rheumatoid arthritis. Histologic changes persisted in subcutaneous and scleral nodules in spite of clinical regression.[73, 157, 301, 1029, 1514, 1555, 2104] Mononuclear and multinucleated giant cells were noted during regression of scleral nodules.[2104] Mucinous edema of ground substance of nodules decreased, an effect resembling the in vitro action of hyaluronidase.[1029] Improvement in the inflammatory changes in skeletal muscle, with disappearance of nodular infiltrates, was noted.[1554, 1555] In one case studied postmortem, amyloid deposits did not appear to have been altered during cortisone administration.[2234]

Route of Administration. The oral administration of cortisone acetate was found to be simple and effective.[222, 224, 702, 931, 2190, 2191] No constant dosage ratio could be established between orally and intramuscularly administered cortisone acetate, but maintenance doses of cortisone were found to be higher by the oral route.[222] Both the free alcohol and the acetate of hydrocortisone were effective by oral administration.[224] For oral use, three or four daily divided doses of cortisone were recommended.[222, 704, 2128, 2191] The implantation of 12 pellets containing 75 mg. of cortisone

to each of eight adult patients resulted in prompt improvement maintained for two to four weeks.[587]

The instillation of cortisone into the conjunctival sac resulted in improvement in ocular manifestations.[532, 990, 1540, 1554] The intravenous infusion of corticotropin was found more effective than intramuscular or subcutaneous injections. [See section on "Pituitary-Adrenal Physiology."—Ed.]

Dosage. The practice of administering excessive initial doses of adrenal hormones was not clearly advantageous and became less popular.[189, 1724, 2189] Accumulating experience indicated that dosage levels should be regulated for optimal and not for maximal results: that is, for the greatest relief attainable without undesirable effects.[932] In general, maintenance requirements were found to vary with therapeutic objectives, with severity of the disease, and with individual responsiveness.[223, 367, 932, 1724]

With cortisone, moderate initial suppressive doses (100 mg. per day) were usually adequate.[2189] In two studies, massive doses of cortisone (500 mg. per day) were given intramuscularly for 14 to 35 days with the objective of suppressing rheumatic manifestations as completely as possible. All patients so treated obtained excellent remissions during the period of administration, and some experienced remissions lasting for several months. Most relapsed, however, in a few weeks or months after the steroid was discontinued, and it was concluded that such dosage had no advantage over the usual levels.[130, 353] Only one group continued to advocate initial dosage to the point of complete suppression, followed by maintenance levels.[1172] [Unfortunately, the results of this plan of treatment are reported only in terms of functional improvement.—Ed.]

In one group of 60 patients, the maintenance dose required for reasonable control of symptoms was stable in 36 (60%); nine of the group required brief periods of higher dosage to control exacerbations. The requirements for satisfactory regulation varied with the severity of the disease. Severe cases required an average of 80 mg. per day; moderately severe cases, 64 mg.; moderate cases, 55 mg.; and mild cases, 37.5 mg.[223] Satisfactory control of the disease was achieved in 100 patients treated at the Mayo Clinic with maintenance doses ranging between 25 and 62.5 mg. per day.[2191] The maintenance requirements of children did not correlate with body size.[702]

Well defined differences in dosage were observed in clinical trials comparing hydrocortisone with cortisone and cortisone acetate. By the oral route, hydrocortisone (free alcohol) was approximately 50% more potent than cortisone acetate, whereas hydrocortisone acetate was somewhat less potent than cortisone acetate.[218, 224] [Most observers would place the advantage of hydrocortisone somewhat lower, at approximately 20% greater potency.—Ed.]

Results of Therapy. There was general agreement that corticosteroid and corticotropin therapy is only suppressive and does not result in lasting remissions.[219, 221, 223, 367, 699, 704, 931] Maintenance cortisone therapy was found beneficial for some, but not practical for all patients.[699] The best therapeutic results were obtained in less severe cases. In a series of 76 cases, treatment was stopped in 18 patients (23%) because of insufficient response in eight, untoward effects in nine, and a spontaneous remission in one. Of 60 patients treated with maintenance doses averaging 69 mg. per day for periods exceeding six months, marked improvement was observed in 48 (80%).[219, 223] In another series of 44 cases, treatment was discontinued at some time in 24 because of poor response or adverse effects, or by election. Of 23 patients in whom treatment was con-

tinued, maintenance doses of cortisone of less than 75 mg. per day for periods of 100 to 400 days were considered to give good results.[704]

In a few studies, the therapeutic results were evaluated according to the criteria recommended by the American Rheumatism Association. [These criteria were presented in detail in the Tenth Rheumatism Review.—Ed.] Corticotropin was administered continuously to 35 patients for periods averaging 9.6 months. In seven patients (20%) complete clinical remissions (grade I) were maintained without untoward effects. Another 14 (40%) experienced worth while improvement (grades II and III), although with adverse effects. Fourteen patients (40%) had no significant improvement (grade IV), many developing unresponsiveness to the drug.[982] In the application of these criteria to results of maintenance therapy in 55 patients, it was found that 5% had grade I response; 27%, grade II; 51%, grade III; and 17%, grade IV.[2032] In contrast, West and Newns found that, in 27 patients maintained on 50 to 75 mg. of cortisone daily for one to three years, none experienced a complete remission, four showed marked improvement, four minor improvement, and 19 were essentially unchanged.[2235] Causes of unsatisfactory results were listed as (1) too rapid reduction of dose, (2) erratic dosage, (3) insufficient dosage, (4) neglect of measures to control adverse effects, (5) failure to use a booster dose, and (6) physical irritation or excessive activity.[932]

Functional improvement was an impressive feature of adrenal hormone therapy. Of a group of 59 patients, only 28 were performing full or part-time work prior to treatment, while 52 were working during maintenance therapy.[1706] In a British study, 17 of 20 patients were enabled to return to previous work or household duties.[432] Total results were more satisfactory when the hormones supplemented comprehensive care, including measures for rehabilitation.[367, 699]

Complications of Therapy. Although some degree of hyperadrenalism was considered a prerequisite for successful adrenal hormone therapy,[1706] the incidence of adverse effects correlated with dosage and with the duration of administration.[222, 223, 704, 1381, 2189] No significant complications occurred in 130 patients receiving doses of 75 mg. of cortisone or less per day,[1381] whereas 17 of 24 patients developed undesirable effects on doses exceeding 75 mg. per day.[223] Females were found more susceptible to complications than males.[704] Troublesome metabolic disturbances and hypertension were observed more frequently during the first few weeks of treatment.[704] The clinical importance of side-effects did not correspond to their absolute incidence. In a study of 128 patients, complications from treatment were considered insignificant in 90% of the 52 patients exhibiting untoward manifestations.[2033] In 60 patients receiving cortisone or corticotropin, 12 (20%) developed a single manifestation of intolerance and an equal number developed multiple manifestations.[223]

The importance of the state of induced hyperadrenalism was emphasized by observations of the poor prognosis of the natural course of 114 cases of spontaneous untreated Cushing's disease. Death resulted in the majority of patients within a five year period.[1668] Several fatalities occurred during or after adrenal hormone therapy for rheumatoid arthritis.[225, 353, 367, 1184, 1381, 1706, 1802, 1830, 1831, 2104, 2234, 2235] [The wide variety of adverse effects observed is reviewed in detail in the section on "The Adrenals and Rheumatic Diseases." With the single exception noted below, the complications seen during and following the use of these agents in rheumatoid arthritis did not differ significantly from those seen in association with their use in other diseases.—Ed.]

Slocumb described a syndrome of "hypercortisonism" seen most frequently in postmenopausal women. It was characterized by cyclic swings through restlessness and exhaustion, and by emotional instability or depression. Complaints of muscle and joint aching easily led to confusion with a flare in the rheumatoid process, although objective findings of such a flare were lacking. If the dosage of cortisone was increased, there was temporary improvement for a few days or weeks, only to have the cyclic swings recur. If the dosage was gradually decreased, the patients usually felt better, with release of tension. In some patients, reduction in dosage led to a severe flare-up which at times closely resembled systemic lupus erythematosus or periarteritis. Such a "pan-mesenchymal reaction" was seen only in patients receiving cortisone for rheumatoid arthritis. The syndrome was attributed to the adaptation of the tissues to large amounts of exogenous corticosteroid rather than to adrenocortical suppression.[1943, 1944] [This pattern of reaction needs further study. Its pathogenesis is far from clear, and the proposed explanation can be examined by suitable studies of blood corticosteroid levels.—Ed.]

Adrenal cortical suppression in patients receiving cortisone for rheumatoid arthritis was of particular concern. The response to 25 mg. of corticotropin, as measured by eosinopenia and increase in urinary steroid excretion, was abolished in all of 11 patients tested in this manner. After treatment, recovery of the eosinopenic response to 25 mg. of corticotropin occurred after intervals ranging from 10 to 80 days.[223] Significant temporary hypoadrenalism associated with asthenia was observed in 40% of patients in one series.[704] The post-treatment period was characterized by asthenia, depression, anorexia and tachycardia, in addition to the manifestations of rheumatoid exacerbations.[189, 702, 704] Although the intermittent or terminal administration of corticotropin was recommended to minimize the dangers of adrenocortical suppression,[2189] experiments with rats[731] and human autopsy studies[1830, 1831] indicated that pituitary suppression is an important factor in cortisone-induced adrenal insufficiency. [This problem is discussed in more detail in the section on "The Adrenals and Rheumatic Diseases." There is a surprising dearth of factual information as to the frequency and dosage of corticotropin injections required to maintain adrenal responsiveness during administration of corticosteroids. There is no evidence that the routine use of ACTH at seven to 10 day intervals during long-term corticosteroid therapy is advantageous. Neither is it essential to administer corticotropin whenever steroid therapy is terminated, although in selected patients judicious use of ACTH may be helpful in controlling symptoms during the withdrawal period.—Ed.]

Conclusions Regarding Corticosteroids and Corticotropin. The literature covered in this Review reflects a period in which the limitations and dangers of therapy with these agents became more sharply defined. As these facts became more widely appreciated, the high hopes held for these agents as a panacea for rheumatoid arthritis gave way to disillusionment in some quarters. The opinion that these hormones yielded no better long-range results than conventional methods of treatment was supported by one study, in which the status of 27 patients who had received moderate doses of cortisone for one to three years was not clearly superior to retrospective but carefully matched control cases.[2235] Some felt that the patients with rheumatoid arthritis were probably not getting as good care as before cortisone. "Instead of going to some centre where arthritis work was being done, the patients stayed home and decided to try cortisone."[1770] Others protested against this wave of pessimism regarding the use of hormonal therapy. "It is more difficult to use properly than was at first

hoped, . . . but we have found it possible to achieve success in the majority of cases if enough time and trouble is taken."[431]

[The criticism that enthusiasm for these agents has led to neglect of standard methods of treatment is unfortunately justified in some degree. Nevertheless, these agents constitute the only rapidly-acting therapeutic weapons which can suppress the signs and symptoms of rheumatoid arthritis in many cases. But they are needed in the management of a minority of patients. Candidates for their use must be carefully selected. The substances are far from foolproof, and experience is needed in their use; the patient's needs and responses must be frequently reviewed. They should always be used in association with other fundamental methods of treatment, rather than depended on as the sole therapeutic measure. With these limitations clearly defined, few physicians caring for patients with rheumatoid arthritis would choose to return to the days when these agents were not available. Nor should their limitations as therapeutic agents blind observers to the tremendous stimulus which their discovery has given to research. Future investigations, stimulated by the knowledge of these hormones, may well provide the long-sought key to the mystery of rheumatoid arthritis, and lead to its eventual conquest.—Ed.]

Intra-articular Cortisone and Hydrocortisone. The intra-articular instillation of both cortisone and hydrocortisone suppressed rheumatoid activity in the treated joint without a significant systemic effect; this effect was more clearly and more consistently obtained with hydrocortisone or hydrocortisone acetate.[532, 990, 2319] Such instillations of hydrocortisone resulted in local amelioration of joint manifestations for variable periods of time.[176, 188, 282, 532, 619, 699, 985, 986, 987, 990, 991, 1080, 1144, 1554, 1685, 1827, 2047, 2258, 2318, 2319] The local effect of hydrocortisone administered in this manner was confirmed by experiments which disclosed consistent reductions of joint temperature,[985] decreases in synovial fluid leukocytes and polymorphonuclear neutrophils,[176, 1144, 2047, 2319] increases in synovial fluid viscosity, [1080, 1144, 2319] increases in hyaluronate concentration,[1080] decreases in synovial fluid aminotripeptidase activity,[2318, 2319] and favorable histologic changes in synovial tissue removed by biopsy.[188]

Studies of the fate of cortisone and hydrocortisone injected into the joint showed that the microcrystals disappeared within two hours, being absorbed (or phagocytized) and retained in the synovial cells.[987] Chromatographic experiments showed disappearance of 85% of the injected steroid in one hour, and 98% in three hours, with no essential difference in the rates of disappearance of cortisone and hydrocortisone. Three distinct chromatographic bands subsequently appeared, suggesting that steroid metabolites were formed locally.[2258] More soluble forms of cortisone, such as the free alcohol and tricarbyllate, were no more effective than the acetate.[991] [Subsequent work suggests that the tertiary butyl acetate of hydrocortisone may have some superiority.—Ed.]

Doses of 25 to 37.5 mg. of hydrocortisone were found effective.[985] From experiences with injections into the knee, ankle, wrist, hip, phalangeal joints, elbow, shoulder, bursae, tendon sheaths, and pleural and pericardial cavities, it was concluded that the procedure was more effective in the more accessible joints. Clinical improvement was observed in 89% of 376 patients so treated. Improvement was manifested in 24 hours and persisted for an average of eight days.[985, 987] With repeated injections, maximal benefit could be extended to 10 to 14 days.[1107] Complications of intra-articular hydrocortisone therapy in a series of 8,696 injections (all diseases) included: local exacerbations, 1.9%; local weakness, 0.2%; general weakness, 0.17%; local urticaria, 0.04%; spread

of rheumatoid arthritis, 0.02%; infectious arthritis, 0.02%; thrombophlebitis, 0.02%; exacerbation of tuberculous arthritis, 0.01%.[987]

[While intra-articular hydrocortisone has significant therapeutic effects, its usefulness is limited in rheumatoid arthritis because of the systemic nature of the disease and the local and temporary nature of the therapeutic effects. Therefore, it is most helpful in patients where one or a few large joints are the main problem in treatment.—Ed.]

Other Steroids. The continuing search for antirheumatic steroids other than cortisone and hydrocortisone made a number of related compounds available for study, although quantities of material were frequently limited. Subjective, and occasionally objective, improvement was observed during the administration of pregnenolone;[692, 927, 982, 1400, 1417, 1444, 1779] 21-acetoxypregnenolone;[487] Δ 5, 16 pregnadiene 3-beta-ol-20-one-acetate; allopregnane 3 beta 21-diol-20-one diacetate; allopregnane 21-ol-3-20-dione acetate;[982] Δ 5, 3 acetoxy etiocholenic acid;[701] testosterone[927] and desoxycorticosterone in combination with ascorbic acid.[322, 1421, 1444] In other clinical trials, insignificant or no benefit was observed during the administration of pregnenolone;[76, 120, 288, 290, 366, 701, 1010, 1289, 1520, 1521, 1539, 1556, 1802, 2268] 21 acetoxypregnenolone;[76, 120, 290, 366, 701, 1268a, 1289, 1369, 1556, 1802] 16 dehydropregnenolone;[120, 366, 1556] allopregnene-21-ol-c, 21, dione acetate;[701] Δ 5 pregnene 3-(b)21-diol-20-one-21 propionol;[701, 1802] 11 desoxy 17 alpha hydroxycorticosterone;[701, 1802] pregnentriolone;[701, 1802] 3, 21 dehydroxy-11-keto Δ 17, 20 cyanopregnene; Δ 5, 17 ethinyl androstene 3, 17 diol;[701] dihydrocortisone;[701] desoxycorticosterone;[366, 1802] saturated desoxycorticosterone;[120] desoxycorticosterone in combination with ascorbic acid;[542, 1305, 1369, 1556, 1669, 2268] testosterone;[366, 701, 1369, 1556, 1802] dehydroisoandrosterone;[366] methyl androstenediol;[1011] progesterone;[366, 1802] 11 ketoprogesterone;[559] 17 hydroxyprogesterone;[701, 1802] estradiol,[120, 366, 701] and corticosterone.[365, 1777] Although in one study experiences with pregnenolone suggested a possible synergistic effect when combined with cortisone,[982] in other studies this steroid had no influence on the rate of severity of exacerbations following the withdrawal of cortisone or corticotropin.[120, 701, 1009, 2009]

Disagreement on the results of clinical trials with various steroid preparations of possible low antirheumatic potency was attributed to the lack of uniform methods and objective criteria for clinical testing; and to failure, or inability because of limited supplies of steroids, to design experiments incorporating the placebo method.[120, 414, 1009] [Such discrepancies afford eloquent testimony to the inadequacy of methods for clinical testing.—Ed.] Such clinical trials have been associated with occasional undesirable side effects such as hypertension, cardiac decompensation and myocardial infarction during the administration of desoxycorticosterone,[1927] and congestive heart failure during pregnenolone therapy.[288]

[Since the period covered by this Review, unequivocal antirheumatic effects have been demonstrated with three synthetic modifications of the cortisone and hydrocortisone molecules. One of these, 9-alpha fluorohydrocortisone, while yielding a remarkable enhancement of antirheumatic properties, proved to have even greater enhancement of effects on electrolyte metabolism—to an extent which has precluded its clinical use in rheumatic diseases. Prednisone, a synthetic steroid which differs from cortisone only by the presence of a double bond between C-1 and C-2 in ring A, has four times the antirheumatic potency of cortisone. It has been used clinically since November, 1954. Its principal advantage is that it does not cause sodium retention or increased potassium excretion when administered in daily doses of 30 mg. or less. With this important exception, prednisone has been found to have the same undesirable side-effects (and contraindications) as cortisone, such as Cushing's syndrome,

mental disturbances, fractures, diminished carbohydrate tolerance, increased nitrogen excretion, cutaneous purpuric manifestations, etc. The appearance or reactivation of peptic ulcer with hemorrhage or perforation is associated with the administration of prednisone at least as frequently as and possibly even more frequently than with cortisone or hydrocortisone. Prednisolone, which bears the same structural similarity to hydrocortisone that prednisone bears to cortisone, has had less extensive clinical use. As yet, there is no evidence that its properties differ significantly from those of prednisone.—Ed.]

Potentiation of Adrenal Hormones. No significant increase in the effectiveness of cortisone was achieved by the concomitant administration of pregnenolone,[702, 1779] pregnentriolone,[702] testosterone,[702, 1684] stilbestrol,[1684] ascorbic acid[1684] or adenosine triphosphate.[702] However, a synergistic effect of pregnenolone was suggested by inconclusive studies of 17 patients, of whom 12 expressed subjective improvement and eight exhibited objective improvement when this steroid was added to their maintenance cortisone program.[982] The combination of insulin and cortisone was found to increase the antirheumatic potency of the latter in limited clinical trials.[934, 1010] Protamine had questionable potentiating effects.[1642] A synergistic effect between cortisone and both tetraethylthiuram disulfide (Antabuse) and para-aminobenzoic acid was claimed,[2245] but other workers found no enhanced effectiveness of corticotropin by para-aminobenzoic acid.[474]

Other Aspects of Treatment

General Measures. *Diet and Vitamins.* Despite the fact that maintenance of adequate nutrition was considered essential, there was no specific diet that could be recommended for all patients.[1928, 1958] Although large doses of vitamins were considered of questionable therapeutic value,[1775] the prescription of a multiple vitamin capsule was advised, if only for psychologic reasons.[760, 1309]

Correction of Anemia. A trial of ferrous sulfate administration by mouth was advised in patients with anemia,[215, 216, 1309, 1310, 1775] although this measure was considered of no value in most patients.[1928, 1958] Women were found to be more likely than men to respond to oral iron. The intravenous administration of special preparations of organic iron salts resulted in increases in hemoglobin levels in a small number of patients.[2084] Jeffrey reported improvement in hemoglobin values in 37 of 50 patients given intravenous iron, but was unable to predict which patients would respond.[1075] Folic acid was considered of value in some patients.[1958]

Repeated transfusions were advised, particularly in early cases, since beneficial results sometimes occurred in addition to the correction of anemia.[216, 760, 1309, 1775, 1928] Garry recommended "red cell mass" transfusions in the management of rheumatoid arthritis, and reported improvement in all of 30 patients who received six to 10 transfusions of the sedimented cells in one pint of whole blood.[733] The risk of homologous serum jaundice in the frequent use of transfusions was emphasized.[233, 1541]

Psychotherapy. Psychotherapy was defined in its broadest sense as giving the patient a definite program, encouragement and medication, and was considered an important factor in the over-all management.[1775] It was suggested that listening to the patient's troubles might make the difference between improvement and progression of the disease.[1901] Obtaining the patient's confidence and educating him as to the nature of his disease were regarded as the first steps in successful management.[703] The role of formal psychotherapy in rheumatoid

arthritis was considered unclear.[1702] [Actually, psychotherapy depends on the needs of the individual patient. This again emphasizes the basic principle of treating the patient as a total individual, not just treating his arthritis. Conversely, the effect of psychotherapy complicates evaluation of therapeutic programs. There are two outstanding variables: the patient and the physician. The latter is *not* a constant.—Ed.]

Chrysotherapy. After 30 years' experience with gold therapy in rheumatoid arthritis, the precise value of this medication is still uncertain. Nevertheless, gold therapy continued to enjoy great popularity in many clinics.[233, 344, 1561, 1949] "It may be said that gold is the one remedy that has survived the blizzard of clinical criticism, but even its reputation is a bit tattered."[567]

Indications. Active peripheral rheumatoid arthritis and palindromic rheumatism remained the only rheumatic diseases in which gold therapy seemed indicated.[216, 288, 1775] [The latter was still regarded by many as a variant of rheumatoid arthritis.—Ed.] Most authors continued to recommend a period of conservative management before utilizing gold therapy. The most favorable response to gold therapy was noted in patients who had had the disease for one year or less,[233, 283, 1969] and in whom atrophic and destructive changes had not yet occurred (stage I). [This statement can be applied with equal validity to any form of treatment.—Ed.] Older patients who had persistent activity also obtained benefit from gold salt therapy in some instances.[216, 1561] The decision to use gold should be made by joint agreement between the patient and the physician.[216, 1561]

Contraindications. Systemic lupus erythematosus, active renal or hepatic disease, ulcerative colitis, blood dyscrasia, hemorrhagic tendency and previously demonstrated sensitivity to the drug were generally regarded as contraindications to gold therapy. Prior serious drug reaction or a tendency toward drug idiosyncrasy in general was considered an absolute contraindication.[216, 1775] Rheumatoid arthritis with coexisting mild diabetes mellitus has been treated cautiously with gold salts with no apparent aggravations of the metabolic defect.[216]

Preparations, Dosage and Methods. The soluble gold salts were usually recommended: Myochrysine (gold sodium thiomalate), and Solganal (gold thioglucose), both of which contain 50% of metallic gold.[74, 215, 216, 233, 1247, 1310, 1561, 1775, 1969] Sanocrysin (gold sodium thiosulfate) was noted to cause pain at the injection site.[1488, 1561] Because of the lack of therapeutic effectiveness, colloidal gold preparations have been discarded by most workers.

They were most often given by the intramuscular route, preferably in the guteal region. Sanocrysin was also used intravenously. Dosage programs were regulated by the metallic gold content of the salt used. A few authors preferred doses of 35 to 40 mg. of gold salt as the maximal weekly dosage.[1309, 1928] Others recommended 15 to 25 mg. as an initial dose, and 50 mg. as the maximal weekly dose.[215, 1775] The program most commonly recommended was: weekly injection beginning with 10 mg. the first week, 25 mg. the second week, and 50 mg. weekly thereafter until a total dose of between 1.0 and 2.0 gm. was given, or until maximal improvement had occurred.[233, 427, 945, 1561, 1607] If no improvement occurred after a total dose of 2.0 gm., further therapy with higher doses was considered unlikely to yield results.[215, 233, 945] When maximal therapeutic effect was obtained, there was general agreement that maintenance therapy should be continued indefinitely, with 25 to 50 mg. every two to four weeks.[215, 233, 427, 945, 1309, 1561, 1775, 1928]

Mode of Action. The mechanism by which gold salts influence the course of active rheumatoid arthritis remained obscure.[287, 945] No evidence of impaired liver function was found during gold therapy.[1149] The relationship of gold-salt-induced

remission to adrenocortical activity did not suggest that the improvement could be attributed to any action on the adrenal cortex. Urinary 17-ketosteroid output was determined bi-weekly in 10 females and five males with rheumatoid arthritis who received gold salts for 14 weeks. Thirteen of the 15 patients improved to some extent during treatment; however, no appreciable changes in 17-ketosteroid excretion occurred in any case.[287] With the hypothesis that gold salt therapy is perhaps a form of "stress therapy," a plan to potentiate the action of calcium aurothiomalate by sodium chloride restriction and acidification with ammonium chloride was tried, but no clinical or laboratory evidence of enhancement of response to gold therapy was noted during this five-month study.[1149]

Results. Several studies recorded favorable short-term results from gold-salt therapy. Of 88 patients who received a total of approximately 1.0 gm. of calcium aurothiomalate over a period of five months, 44 were "much improved" at the end of treatment; this was maintained in all but three after an additional three months.[1149] With gold sodium thiomalate, 24 of 26 patients were considered improved in one series,[945] and 26 of 29 (with 17 in remission) in another series.[1561] One of the largest groups studied was 620 patients (386 females and 234 males) in Sweden: of these, 70% had had their disease for more than five years. Sixty-one per cent showed improvement at the completion of therapy, and 26% were unimproved.[1564] [Results in the remaining 13% were not stated.—Ed.] The results in 19 patients treated with gold thioglycolanilid were contrasted with those in 11 patients treated with anti-reticulocytoxic serum or saline injections. No essential differences in the end results were noted, and it was concluded that gold thioglycolanilid, like other insoluble gold salts, had no therapeutic effect.[1488]

The results of studies using patients treated by other methods as controls, and using longer periods of follow-up, were less encouraging. In one such study, 38 patients were treated for 13 weeks with gold sodium thiomalate and the results evaluated at the end of three months and of one year. Adjusting the data to exclude elderly patients, 62% were subjectively improved and 28% objectively improved at three months; 53% were subjectively improved and 30% objectively improved at one year. However, almost exactly the same percentages of improvement were obtained in comparable groups receiving, respectively, copper salts, saline, arsenical preparations, physiotherapy or aspirin.[283] Snorrason in Denmark compared the course of the disease for one to 10 years following treatment with gold sodium thiosulfate in 295 patients, as contrasted with 169 patients treated by other measures. In patients with capsular involvement only, 77% of the gold-treated cases were considered arrested at the end of four years, as compared with 22% of the control group. But the differences became less marked year by year, and at the end of 10 years nearly all patients in both groups showed progression of the disease. In patients in whom the disease was in a later stage of progression at initiation of therapy, there was similar decrease in difference between gold-treated and control groups as the years went by.[1969]

In an important report on the long term course of 123 patients receiving "maintenance" gold-salt therapy, Ragan found no difference between the eventual status of these patients and of those treated by other methods. These patients were observed for an average of eight years and had received gold for an average of five years, with an average total dose of 3.3 gm. of gold salt.

Twenty per cent developed flexion contractures during the period of observation. Of 143 patients who were seen and treated in the first two years after the onset of arthritis, no differences were found between the 68 treated with gold and the 75 receiving other therapy. It was concluded that a gold-induced remission cannot be extended indefinitely, and that gold therapy does not alter the ultimate course of the disease.[1702] [A critical evaluation of the results of gold therapy, both immediate and long-term, is at present impossible. Only a few authors have grouped their cases and results according to an accepted classification. Many have not been specific about the dosage program or the drug used, the total amount of drug given, regimen of maintenance therapy, or term of follow-up. The shortcomings of clinical trials were pointed out in some of these studies.[283, 1488]—Ed.]

Toxicity. Stomatitis, dermatitis, encephalopathy, neuropathy, pruritus, nephritis, jaundice, alopecia, thrombocytopenic purpura, aplastic anemia, agranulocytosis and anemia were again listed as potential toxic reactions to gold.[132, 215, 550, 683, 945, 1247] Fatal thrombocytopenia was reported to have occurred 10 months after gold therapy.[1989] In the series reported, the total incidence of toxic manifestations was 6.6% of 29 cases,[1561] 14.3% of 28 cases,[1488] and 20% of 26 cases.[945] In the largest series, toxic manifestations appeared in 40% of 762 courses of treatment, but they were severe enough to require suspension of treatment in only 6.8%; there were two deaths (0.26%).[1564] [This study covered the period from 1932 to 1946.—Ed.] In another series there had been seven deaths among 575 patients treated (1.2%), but no fatalities related to gold therapy had occurred at this hospital since 1936.[1969] In other series, complications requiring cessation of gold administration were recorded at 2%[1372] and 10%.[1149, 1969] In a comparative study using large doses (200 to 300 mg. per week) the frequency of stomatitis was considerably higher in patients receiving sodium aurothiomalate as compared to those receiving sodium aurothioglucose, but there was no significant difference with respect to the frequency of skin eruption and albuminuria.[1247]

Prevention and Treatment of Toxic Reactions. Cecil's observation that gold toxicity is not preventable remains true; however, vigilance by the prescribing physician for major toxic features is imperative. Therapy should be stopped at the first suggestion of difficulty. Weekly visits which include careful questioning, examination of the mouth and skin, a complete blood count and urinalysis were advised.[427, 945, 1775] Some authors suggested that the blood studies be done at two to four week intervals.[1234, 1310, 1561, 1928] British anti-Lewisite (BAL) and ACTH or cortisone were recommended for the treatment of gold toxicity.[74, 132, 215, 216, 683, 945, 1775, 2025] Two cases of dermatitis due to gold sodium thiomalate failed to respond to adequate BAL therapy but subsequently cleared on ACTH and cortisone.[132] A case of thrombocytopenic purpura which failed to respond to 21 injections of 1.5 ml. of BAL in oil over a 10-day treatment period was cited. In a patient who developed thrombocytopenic purpura several months after the successful treatment of a gold dermatitis with BAL, splenectomy was followed by prompt improvement. Splenectomy also seemed to benefit a patient with a pancytopenia directly related to gold salt therapy.[2207] A patient with moderately severe polyneuritis recovered in two months with only conservative measures.[550] Cortisone acetate and phenylbutazone did not influence the chronic toxicity of soluble gold salts in albino rats.[837]

Results of Combined Gold and Hormonal Therapy. There was no clearcut

demonstration of synergistic or additive therapeutic effects when gold was given in conjunction with ACTH or cortisone. Some authors simply stated that combined therapy in their hands had been unsuccessful.[1032, 2189] Others reported encouraging results in a small number of cases.[233, 618, 807, 1539, 2119] Encouraging results were reported in 19 patients treated simultaneously with cortisone and gold salts.[618] Similar favorable results were reported in 12 patients who received an initial 10-week course of 500 mg. of aurothioglucose followed by a 10-day course of cortisone. Then gold therapy was continued until a total dose of 1 gm. was reached.[233] Thompson and Rowe added cortisone to the program of eight patients who were only partially responding to gold salts, and treated an additional 13 patients concurrently with the two agents. The therapeutic response was considered excellent, but the effectiveness appeared no greater than that expected with chrysotherapy alone after the steroid was discontinued.[2119] In one case, dermatitis, stomatitis and hepatitis appeared shortly after the termination of nine days of ACTH administration during a course of gold therapy.[1427] [Subsequent experience indicates no real evidence of either a potentiating or antagonistic action between corticosteroids and gold salts. While it is at times expedient to use the two agents concurrently, the results do not appear to differ significantly from those obtained with gold salts alone. Concomitant corticosteroid therapy does not lessen the need for the usual precautions when gold salts are used.—Ed.]

Conclusions on Chrysotherapy. Gold salts therapy has now been used in rheumatoid arthritis for more than 20 years, so there has been time to assess its value. The only thing really settled is that there is an agreed dosage and timing in administration.[74] However, the facts that our knowledge of gold is incomplete and that results are subject to argument were not considered logical reasons why one should lack the courage to use it in adequate doses whenever it may be indicated. The middle ground—of regarding gold as a useful therapy of probable but not scientifically proved effectiveness—seemed reasonable to some observers.[427, 1702, 1775] However, many authors continued either staunchly to advocate [945, 1234, 1541, 1561] or definitely to question [283, 1949] the value of this drug.

Whatever the viewpoint, gold therapy should not be considered the final answer to the problem of therapy in rheumatoid arthritis.[1928] The many failures, and the constant risk of toxicity attending its use, make the drug basically unsatisfactory and furnish "a sharp reminder that gold, in common with all other drugs, affords no short cut to the treatment of rheumatoid arthritis, and that it is no substitute for the proper management of these patients. Treatment must include, in particular, the prevention of joint deformity and the maintenance of muscle power and joint range. Gold must not divert our attention from these fundamental principles."[49]

Other Special Measures. *Measures Directed Against Infection.* Aureomycin, Terramycin and chloramphenicol, used in very small doses over long periods of time, were reported to be of benefit in rheumatoid arthritis.[2243] Following the observation that 92% of 101 patients with rheumatoid arthritis were infected with *Endamoeba histolytica*, anti-amebic therapy was instituted with reported benefit.[1757] [To our knowledge, no confirmation of a relationship between amebiasis and rheumatoid arthritis has appeared.—Ed.] The extraction of infected teeth was not found to affect the subsequent development of polyarthritis in a series of 346 patients.[200] In the belief that rheumatoid arthritis is caused by bacterial allergy, workers have reported benefit from

long-term desensitization with Crowe's vaccine[1649] and with filtrates of hemolytic[204] and of nonhemolytic streptococci.[1945]

Antispasmodics. Encouraging results have been reported in small series of patients with rheumatoid arthritis treated with drugs which act upon the autonomic nervous system. Two of five patients improved with methane sulfate of hydrogenated ergot.[2072] Tetraethylammonium chloride was reported to be of benefit in five cases.[1627a, 1657] Tetraethylammonium bromide relieved pain and swelling due to exacerbations of rheumatoid arthritis in 20 cases.[1021] Several cholinergic drugs gave marked relief of muscle spasm and were recommended as adjuncts to other therapy.[385] Mephenesin was reported to be effective in relieving muscle spasm in 32 of 50 rheumatoid patients.[941] [Data documenting these effects are not impressive.—F. I.]

H. P. C. (Hydroxy-phenylcinchoninic acid). This compound was used in controlled clinical trials in patients with active rheumatoid arthritis. Although excellent analgesic results were reported in the majority of patients treated, the high incidence and severity of the side-effects, notably photosensitivity and gastrointestinal disturbances, made this agent unfit for widespread clinical use.[597, 1362, 1934]

Postpartum and Placental Plasma. Granirer, who first proposed in 1949 the injection of pooled postpartum plasma as therapy in patients with rheumatoid arthritis, summarized the clinical observations in eight patients so treated and followed over a period of two years. These patients required six to eight pints of postpartum plasma, given in amounts of 250 ml. once a week, to produce a remission. Clinical improvement was associated with a return to normal of the hemoglobin and the serum albumin and globulin, while the sedimentation rate usually remained elevated. Remissions were observed to last from six weeks to 18 months. In more than 500 treatments, there was stated to have been no instance of homologous serum hepatitis.[815] The presence of significant amounts of corticotropin and of adrenocorticosteroids in postpartum plasma was demonstrated by bio-assay and paper chromatography; neither hormone could be detected in normal plasma by these methods.[816] The high level of 17-hydroxycorticosteroids in postpartum blood was confirmed by others.[739] Other workers failed to obtain any significant effects from postpartum plasma collected and administered according to Granirer's technics.[1545] [Two of us, J. J. B. and B. M. N., have also obtained negative results with postpartum plasma. It is obvious that the hormones which have been demonstrated in postpartum blood cannot explain more than a transient ameliorating effect.—Ed.]

The repeated administration of small quantities of placental serum was reported to result in objective and subjective improvement.[67, 521, 1282, 1993] Placental blood was collected immediately postpartum, separated by centrifugation and sterilized by passage through a Seitz filter. From 5 to 250 ml. were administered intravenously or intramuscularly at one to seven day intervals.[1993] Others used 10 ml. twice a week.[1282] In one group of 15 patients, complete remission (grade I response) was obtained in three, response was classified as grade II in three, as grade III in four, and five were unimproved. In the 10 who improved, results were maintained without additional therapy.[1993] In another series totaling 47 patients, no complete remissions were obtained; 31 had grade II response, 10 grade III, and six were unimproved.[1282] Control studies with normal plasma were stated to have shown no effect.[815, 1282, 1993] [The details of the control observations are not recorded.—Ed.] The effectiveness of placental serum therapy was left in doubt by Simson and Bunim, who observed mild

improvement in only two of eight patients treated for eight to 12 weeks; four were unchanged, and two were worse.[1935] [Therapeutic properties of placental serum are unproved.—Ed.]

Vitamin D. Few physicians recommended high doses of vitamin D. The potential danger of excessive amounts of vitamin D was again emphasized.[5, 350, 358, 2222, 2253] The roentgenologic findings in five cases displayed generalized osteoporosis and periarticular calcifications due to hypervitaminosis D.[358] Data from 111 previously reported cases and from seven cases seen at the Massachusetts General Hospital were analyzed.[350]

Trials with Other Agents. Insulin-induced hypoglycemia, used to stimulate the pituitary-adrenal mechanism, resulted in temporary improvement in 82% of 72 cases, but most relapsed within a few months;[774, 1150] serious unexplained disturbances of carbohydrate metabolism occasionally followed its use.[1151, 1933] Isolated reports have claimed relief of symptoms with para-aminosalicylate,[278] mepacrine,[690] chloroquine diphosphate,[919] thiouracil,[1068] and several synthetic hyaluronidase inhibitors.[873] Five of six patients with rheumatoid arthritis reported subjective improvement with either repository heparin or Paritol-C (an oral anticoagulant), and four showed objective improvement.[1020] Workers using large doses of para-aminobenzoic acid (12 gm. daily) with 2.6 gm. of salicylates reported slow but progressive functional improvement in 34 of 44 patients with rheumatoid arthritis.[2311] [Several of us have not been impressed with the changes observed in patients with rheumatoid arthritis who were receiving anticoagulants, or large doses of para-aminobenzoic acid with or without salicylates. Improvement, when it occurs, is largely subjective and does not differ substantially from that seen on more conventional programs of management.—Ed.]

Critical trials with several agents yielded negative results. Adenosine triphosphate given intramuscularly was found to have no effect in 11 of 12 patients.[773] Roentgen therapy was reëvaluated in well controlled series and was again found to be disappointing.[515, 964] Procaine and procaine amide (Pronestyl) were given orally, intravenously and intra-articularly to patients with rheumatoid arthritis, with equivocal results.[146, 2136] Carefully controlled studies of pain relief by intravenous procaine led to the conclusion that "unless this drug can be demonstrated to produce significant beneficial results on specific disease processes, it has no place in the treatment of pain."[1116] In a carefully controlled "double-blind" study, there was no significant advantage from administration of creatine precursors (glycocyamine and betaine) to patients with rheumatoid or any other type of arthritis.[958]

Temporary antirheumatic effects were reported during the use of drugs which produced serious toxic effects. Primaquine appeared to provide improvement in 21 hospitalized patients, but the high incidence of side effects (methemoglobinemia, anorexia and neutropenia) made its continued use inadvisable.[2013] Theoretic considerations led to clinical trial of nitrogen mustards[1648, 1914] and aminopterin[853] in small groups of patients; temporary clinical improvement was reported, followed by relapse in a few weeks. Significant toxicity accompanied the suppressive effect of aminopterin.[853]

Splenectomy. The subsequent course was evaluated in 12 patients with rheumatoid arthritis in whom the spleen had been removed at some time during the previous 12 years. After operation there was improvement in general health, with relief of joint pain, stiffness and swelling. The laboratory findings showed a reversal of certain abnormalities. However, splenectomy was not advocated as a form of therapy in this disease.[85] In the literature, Steinberg found 46 published reports (37 patients) on the value of splenectomy in rheumatoid arthritis and added three case reports of his own. It was theorized that splenectomy may set in motion a mechanism resulting in an increased release of corticotropin.[2023] [Studies of the course of rheumatoid arthritis following splenectomy should make a sharp distinction between the effect on the joint

disease and the effect on the hematologic abnormality for which this operation is usually done.—Ed.]

Physical Therapy. To attain the objectives of physical medicine in rheumatoid arthritis, it was considered inadequate to provide treatment in the hospital, office or clinic; proper instructions for similar procedures in the home were of prime importance.[585, 1817] The indications for and technics of application of the physical therapeutic modalities of rest, heat, massage and exercise, alone and in combination with cortisone and ACTH, were discussed.[97, 585, 625, 760, 1547, 1817] General rest was of special significance when weight-bearing joints were involved, and local rest of the more painful joints by the application of splints was suggested.[97] If prolonged rest in bed is required, exercise therapy should be started while the patient is still in bed. Also, with bed patients, particular attention should be given to preventing contractures, by use of proper positioning and support.[585] The efficiency and practical usefulness of various means of applying heat were studied.[747, 1817, 2240] Massage was of limited value in the treatment of arthritis.[97] When used correctly, exercise was considered to be by far the most important agent in the treatment of arthritis.[97, 625, 1817] The types of exercise (i.e., active and passive) were defined and the value of these in the prevention of deformities, reduction of pain, and the relief of muscle spasm was reviewed.[97, 1140] Erickson advocated active movement as soon as any degree of movement was possible, utilizing active assistive exercise as soon as the patient can move the joint through a full range of motion.[625] Simple finger flexion exercises to correct deformities of the arthritic hand were worked out.[96, 2034] Another device to overcome the ulnar deviation of the fingers consisted of simple cotton gloves to which were attached hooks and eyes in such a fashion that rubber bands could provide continuous traction.[1792]

The introduction of cortisone and corticotropin as therapy for rheumatoid arthritis has not eliminated the need for physical therapy. There was general agreement that these hormones effectively reduce stiffness, swelling, tenderness and pain, but that they do not repair damaged joints.[1670, 1792, 1970]

Rehabilitation of the Rheumatoid Patient. There was an upsurge of interest in the role of physical medicine in the rehabilitation of the patient with rheumatoid arthritis. Many reports reflected an optimistic outlook even for those who were chronically disabled.[97, 438, 585, 625, 1331, 1547, 1670, 1705, 1817, 1970] Factors to be considered in the total evaluation of the patient's potential for partial or complete productive employment were presented.[473, 1331] A comprehensive plan of rehabilitation was needed which included specialized physiotherapy, occupational therapy, the use of drugs, surgical correction, individual or group psychotherapy, and prevocational counseling and training.[473] The practical limitations of rehabilitation efforts in rheumatoid arthritis centered around permanent deformities and secondary hypertrophic changes in the joints, individual steroid tolerance and psychologic factors.[1332] The director of a large institute for rehabilitation stated that success in returning arthritics to employment depends upon (1) paying attention to the residual capacities of the individual; (2) stimulating the patient to make use of his own physical capacities; (3) providing the individual with those technics which will teach him to work with his residual disabilities; (4) changing the attitude of the employer to one of willingness to hire the handicapped arthritic worker.[1154]

Nonsurgical Orthopedic Measures. Emphasis was placed on physiologic rest obtained by adequate splinting in the early stages of rheumatoid arthritis.[829, 752, 1828] Favorable preliminary impressions were recorded of the results obtained by more prolonged and complete immobilization of painful and swollen joints at the initiation of treatment.[567, 1140] [Documented reports of the value of this departure from usual management will be of interest.—Ed.] If deformity had already occurred, the joint was splinted in the position of optimal function; as spasm subsided, the joint could be brought into better position with a new cast.[407, 752, 1202] There was general agreement on plaster of paris as the cheapest and most adaptable material for splinting joints; acrylic splints were useful for the rheumatoid hand.[752, 1135] Splints that could be removed several times a day for exercise and for the application of heat were advantageous.

Since bones in rheumatoid arthritis break easily, any manipulation should be performed with great care. Adhesions, whether periarticular or intra-articular, may be successfully treated. The joint should never be manipulated before four to six weeks have elapsed following the onset of the trauma or inflammation. Physiotherapy should be instituted immediately after the successful manipulation.[758, 1202, 1682] Steindler rejected forcible manipulation for the wrists and fingers.[2036]

Surgical Procedures. Law listed as procedures permissible in the active or early phase of rheumatoid arthritis: excision of the acromion, excision of the radial head, and synovectomy of the knee. He felt that other operations, such as radiocarpal fusion, arthroplasty and arthrodesis of elbow, hip and knee, and surgery of the feet, should be deferred until the intermediate or late stages of the disease.[1246] Renewed interest in arthroplasty of the knee was evidenced by favorable reports on nylon as an interposed membrane.[1202, 1205] Good end results were reported with this procedure in 33 of 38 patients with severe pain and disability due to joint destruction, and in 15 of 18 with bony ankylosis.[1207] Preston obtained good results in nine of 11 patients in whom rheumatoid knees were reconstructed, with attention directed to obtaining full extension, restoration of the motor extensor apparatus, and removal of causes of impairment of motion in the anterior intra-articular compartment.[1683] The results of 37 fascial arthroplasties of the knee were good in 11 patients, fair in eight and poor in 18. In this series, patients with ankylosis due to polyarthritis of rheumatoid type were poor candidates, and the most favorable results were obtained in patients in whom a single knee joint was involved secondary to an infection.[1469] A new operative procedure on the knee with the interposition of a metallic cap was described.[758]

In comparatively few cases of rheumatoid arthritis were there benefits from synovectomy, whereas in the hypertrophic or post-traumatic cases approximately 75% of the patients did well.[1360a, 1644]

The results of cup arthroplasty of the hip were evaluated two and one-half to four years after surgery in 38 patients (61 hips). There were early complications in nine, intermediate in five, and late in 11; six required manipulations for adhesions, and six required revision because of re-ankylosis. While most patients were helped and given a limited range of useful motion, the results were not so good as in osteoarthritis of the hip.[1246] [In this report, results in 14 patients with rheumatoid arthritis (21 joints) and in 24 patients with ankylosing spondylitis (40 joints) are grouped together. —Ed.] Arthroplasty of the elbow with the interposition of a free fascial transplant was reported to be "routinely satisfactory." The only definite contraindication was tuberculosis.[1346] Extension contractures of the metacarpophalangeal joints were corrected by the removal of the metacarpal heads.[2036] Arthrodesis of the knee or wrist was recommended for severe painful arthritis caused by trauma or infection. This operation was recommended for overcoming both deformity and pain in the wrists.[1644, 2036] The hammer-toe deformity may be prevented by supporting the metatarsal arch

with a foot plate or by corrective exercises; severe deformity, however, required the removal of the distal half of the proximal phalanx. When there is bony ankylosis, osteotomy may be used in the knee or foot or spine to provide a more useful position.[407, 1202]

Course and Prognosis of Rheumatoid Arthritis

Neither economic status[1967] nor old age[344] influenced the course of rheumatoid arthritis. In the experience of one clinic, treatment (exclusive of corticosteroids) did not alter the natural course of the disease.[1702] The fluctuant life-cycle of rheumatoid arthritis was well exemplified by a seven-year study of a patient during an initial period with active disease, followed by a spontaneous remission, a postoperative exacerbation, a corticotropin-induced remission, and two corticotropin-withdrawal exacerbations.[751] The disease process was active and progressive for about two years. Gradually, the criteria of active disease disappeared. There was a close correlation between the clinical manifestations and the serum protein fractions, as determined electrophoretically. The complete restoration of the protein fractions to normal was the outstanding laboratory feature of the spontaneous remission. In spite of this, the disease process was still active, as shown by the persistence of moderate synovitis. During the administration of corticotropin, changes occurred in the clinical and laboratory manifestations of rheumatoid arthritis comparable to the spontaneous remission, save for the persistence of moderately severe anemia; again, there was persistence of moderate synovitis. Thus, most of the manifestations of disease were held in abeyance through both the spontaneous and the corticotropin-induced remissions, but the underlying disease process was not eradicated.[751] In another study, synovitis persisted for periods of 40 years or more; "burned-out" rheumatoid arthritis was regarded as uncommon.[755]

The mortality rate for persons with rheumatoid arthritis was 24.4 per 1,000 patient-years, as compared with 18.9 for persons of the general population of comparable age and sex. The higher mortality rate was due to the fact that younger arthritics, particularly male, succumbed more rapidly than expected; longevity was not apt to be altered after the age of 50 years. Notable for their frequency as causes of death among rheumatoid patients were valvular heart disease, infections, renal disease and pulmonary embolism; notable for their absence or infrequency were accidental deaths, hypertensive heart disease and myocardial infarction.[381]

Rheumatoid (Ankylosing) Spondylitis

In the United States, many authors designated rheumatoid (ankylosing) spondylitis as a variant of rheumatoid arthritis.[408] Others, including a number of British rheumatologists, considered them to be separate and distinct diseases.[430, 903, 1609, 2149] The occurrence of peripheral joint involvement indistinguishable from classic rheumatoid arthritis in 20% of patients was considered a strong point favoring a common identity. However, a higher incidence of spinal condition in males, the ineffectiveness of chrysotherapy and the greater effectiveness of x-ray therapy in spondylitis were seemingly important distinguishing features. The serologic tests for rheumatoid arthritis were generally negative in patients with spondylitis.[408, 430] [This debate is still in progress.

Available information does not allow settling the question conclusively, and it is necessary to keep an open mind. Further long-term studies and other investigation may eventually provide the answer.—Ed.]

Accurate information concerning the incidence of this condition in civilian populations is scarce. Holst and Iverson obtained such data in a Norwegian county with a population just under 150,000. The patients were located through hospital and practitioner's records and the diagnosis was confirmed by review of roentgenograms. During a 16-year period (1933–1949) the diagnosis of spondylarthritis ankylopoietica was made in 95 men and 21 women. The incidence for the entire county in the inhabitants over 20 years of age was 1.73 per thousand men and 0.38 per thousand women. It was felt that the best estimate of incidence was obtained in the largest town in the county, where the figures in the same age group were 3.11 and 0.6 per thousand in males and females, respectively.[1006] [More information of this type is needed, but it is difficult to obtain.—Ed.]

Most writers agreed that rheumatoid (ankylosing) spondylitis occurs mainly among young male adults, usually with the onset between the ages of 20 and 40 years.[417, 1522, 1609] The predominance among males was again noted, with the sex ratio ranging from 4:1 to 10:1.[217, 1215, 2151] An exception was observed among 100 patients with ankylosing spondylitis in the eastern states of Australia; in this group 43% were women.[1609] [This series was drawn from a population in which 65% were women. While 10% of the patients were diagnosed in the "pre-spondylitis stage," these patients were followed carefully and eight of the 10 subsequently developed roentgenographic changes in the sacro-iliac joints. It seems unlikely that variation in diagnostic criteria accounts for the unusual sex ratio in this series.—Ed.]

The cause of rheumatoid spondylitis remains unknown. Most students of this condition minimized the possible importance of trauma and infections as etiologic factors, but some accepted them as possibly important precipitating or predisposing factors.[417, 1609, 2012, 2237] Personality evaluation of 25 spondylitics reportedly showed a consistent pattern of psychodynamics, featured by intense narcissism. Symptoms appeared to revolve around repression and inhibition of hostile feelings, and were considered to be an expression of markedly inconsistent goals and ideas of the world.[252] [It is the opinion of the reviewers that patients with spondylitis show a range of personality features similar to that found in the general population.—Ed.]

Genetic Factors. Several reports noted the occurrence of multiple cases of rheumatoid spondylitis in certain families.[1215, 1385, 1609, 2040] Of the 13 children of a woman with spondylitis, two daughters and a son had spondylitis, and three other daughters and a son had arthritis. A son and a daughter of one of the above spondylitic daughters also had the disease.[1750, 1964] Occurrence of this condition in identical twins was considered to have established the effect of heredity.[2040] If rheumatoid spondylitis were not inherited, this condition would be expected on the basis of chance to affect identical twins only once in a billion births.[2008]

In recapitulation of an important study, the incidence of rheumatoid spondylitis among 257 relatives of 50 spondylitis patients was calculated to be 30 times as great as the incidence among 2,525 relatives of 406 control families. The condition appeared to be inherited as an autosomal dominant gene, with penetrance of 70% for men and 19% for women. The actual incidence of the disease in 80 sibling pairs was in agreement with this sex difference in penetrance.[2008] [Penetrance is defined

as the ratio of the number actually affected compared to the number expected to be affected. —Ed.] Spondylitis was not believed to be transmitted as a sex linked character. It was suggested that discovery of factors modifying or accelerating the onset of the disease might make it possible to prevent or delay its development.[1962, 2008]

Clinical Data. Symptoms and physical findings of rheumatoid spondylitis were reviewed.[217, 417, 611, 1157, 1522, 1609, 1640, 2149, 1964, 2303] The onset of low back pain was insidious in 80% of the patients, and usually was associated with "stiffness" on first arising in the morning. Sciatica, either unilateral or bilateral and seldom extending below the knee, characterized the onset in 10%. Occasionally radicular pain simulated intra-abdominal disease. In rare instances, progressive stiffness and limitation of motion were noted without pain. Late symptoms and signs depended on the severity, duration and extent of the process, as well as the degree of activity at various levels of the spine. Patients with extensive involvement often retained their weight, had a healthy appearance and complained only of pain. On the other hand, in some patients the disease was very acute and was associated with rapid loss of weight, weakness, severe pain, stiffness, fixation of the chest and progressive deformity which led to ankylosis of the spine and incapacity in one to three years.

Fever was unusual unless the patient had associated rheumatoid arthritis of peripheral joints. Iritis was observed in 5 to 10% of the patients.[217, 1609] In the course of a year, one group found 11 instances of ankylosing spondylitis among persons who sought medical attention for iritis.[193]

Rheumatoid Spondylitis in Women. When a group of 60 women with severe Marie-Strümpell (rheumatoid) spondylitis observed during a period of 20 years were compared with more than 450 men with this disease followed in the same clinics, the disease generally was found to behave similarly in both sexes. Systemic manifestations were somewhat milder in females, and involvement of the cervical region (41 of 60 women) and of the symphysis pubis was more frequent. Familial incidence among these women was 10%. Sciatica, iritis, rheumatic fever and chorea were observed. Three patients had psoriasis; six showed cardiomegaly. Subcutaneous nodules were not observed. While mild cases were readily overlooked or misdiagnosed, this did not account for the infrequency of the diagnosis in women.[2151]

Several points of interest regarding pregnancy in spondylitic women were reported. Pregnancies occurred in some patients with severe involvement of the spine, but took place more often in those with milder disease. Symptoms may first be noticed during pregnancy or may be aggravated by pregnancy. Although a few patients noted some improvement during pregnancy, this was not nearly so common as in the peripheral type of rheumatoid arthritis. Ankylosis or marked limitation of motion sometimes necessitated cesarean section, but most of the reported patients had normal deliveries.[905, 1215, 1609, 2021, 2151] There were no reports of pulmonary complications or respiratory distress, even among patients with fixation of the thoracic cage and diminished vital capacity.[905] [The characteristic fixation of the thorax in expiration with dependency on diaphragmatic breathing certainly must be a handicap during the last trimester, when the uterus rises high in the abdomen.—Ed.]

Complications. A study of 352 patients with ankylosing spondylitis disclosed clinical evidences of cardiac disease in 16 (4.3%). Ten patients showed signs of chronic valvular disease, six having aortic insufficiency. Heart block

was found in three. Of 190 electrocardiograms, 47 were abnormal, with prolonged conduction time the most frequent abnormality.[173] Findings of aortitis and aortic valvular endocarditis were again reported in patients having had spondylitis and peripheral rheumatoid arthritis. Clinical and pathologic features were considered sufficiently characteristic to exclude syphilis and rheumatic heart disease as possible causes.[123]

Gradual appearance of rotation and flexion deformities in the cervical region due to spontaneous dislocations was reported. This appeared during the active phase of the disease, when hyperemia and capsular distention were associated with muscle spasm, thus leading to subluxations.[1195] Death due to medullary compression by the odontoid process which had herniated through the foramen magnum was reported.[486]

Laboratory Studies. Accelerated erythrocyte sedimentation rate, anemia and leukocytosis occurred less frequently than in classic rheumatoid arthritis. In one series the sedimentation rate was normal in nearly half of the patients.[1609] [The usual experience is that about 20% of patients with spondylitis have a normal sedimentation rate.—Ed.] The plasma fibrinogen level was usually slightly elevated and, although there were exceptions, the plasma protein levels fell within the normal range.[1609] In several patients the rate of urinary methionine excretion was lower than normal. This rate sometimes increased as the patient's condition improved.[1609] Serum polysaccharide levels were usually within the normal range.[1902] Determinations of urinary 17-kesteroid excretion in patients with ankylosing spondylitis revealed no significant differences from normal controls.[2230]

In studies of the reaction with sensitized sheep cells, whereas 89.5% of 312 patients with rheumatoid arthritis showed agglutination in dilutions of 1:64 or higher, only two of 22 patients with spondylitis showed agglutination in dilutions greater than 1:32.[2079] In another study only three of 203 cases (1.5%) of spondylitis had positive reactions by this test.[101, 1125] [This finding has been cited as evidence that rheumatoid arthritis and ankylosing spondylitis are different diseases.—Ed.]

Roentgenograms. Initial changes in practically every instance were noted in one or both sacro-iliac joints. Subchondral bony outlines became "blurred," presenting an appearance resembling ground glass, and the sacro-iliac joint spaces appeared to be widened. In the intermediate stage, cancellous bone adjacent to these joints became sclerotic and showed spotty demineralization, resulting in a mottled appearance. In the late stage complete obliteration of the joint may occur. Similar involvement of the apophyseal joints of the lumbar region during early stages required oblique views for optimal visualization. Calcification of paraspinal ligaments was a later manifestation, involving either isolated segments or the entire spine.[217, 417, 452, 1522, 2237] Irregular lytic defects in the pelvic bones, with irregular zones of increased bone density and "whiskering" of the bone periphery, were described; such changes were occasionally seen in vertebrae and extrapelvic bones.[856] Direct injection of contrast media into intervertebral discs showed abnormality in 39 to 74 discs visualized in 30 patients with ankylosing spondylitis.[1784] [It has been generally accepted that the intervertebral discs are normal in this disease. Certainly preservation of disc space is characteristic of usual roentgenographic studies.—Ed.]

Two papers directed attention to involvement of the manubriosternal articulation in rheumatoid spondylitis. Roentgenographic changes resembling those in sacro-iliac joints were demonstrated in 47 of 61 patients[1840] and in 22 of 57 patients.[1984] The corresponding incidence of abnormality in this articulation in nonspondylitic

control subjects was 6 and 5.5%. At first, the joint outline of either the manubrium or the sternum, or both, was lost. Later, erosion of both bone ends was noted. Eventually fusion occurred, first at the periphery, and progressing slowly so as finally to involve the entire joint. Ossification of the symphysis pubis also occurred.[1840] Postmortem radiographs of the skeleton in one patient with extensive spondylitis revealed fusion of the manubrium and xiphoid with the body of the sternum, as well as fusion of the symphysis pubis.[2012] [Involvement of the sternomanubrial articulation in ankylosing spondylitis is apparently more common than is generally appreciated. One of us (D. C. G.) has found clinical and x-ray evidence of involvement of this joint in 15% of 150 patients with spondylitis. Occasionally, pain and tenderness due to such involvement may be severe. —Ed.]

Pathology. Systematic studies of the sacro-iliac joints removed at autopsy showed changes with age comparable to those seen in peripheral joints. The sacro-iliac joints from a patient with spondylitis showed thin islands of cartilage as the only remnant of the joint tissues. Intervening bone showed no evidence of inflammation, fibrous replacement, capsular tissue or synovial tissue.[1351] Comparable changes were observed in two additional specimens.[457] Biopsy of the sternomanubrial joint in five patients showing roentgenographic abnormality revealed extensive replacement of fibrocartilage by collagenous fibrous tissue which spread into the bone, and a striking absence of inflammatory reaction. The changes in this articulation were considered similar to those which occur in the sacro-iliac joints, and the accessibility of the manubriosternal joint was pointed out as a convenient source of pathologic material.[1840]

The characteristics of the pathology in the diarthrodial joints (chiefly axial and limb girdle articulations) obtained at necropsy or operation from 12 patients with spondylitis were interpreted as showing first a subacute or chronic inflammation, including congestion, edema, thickening and proliferation of the synovia. Granulation tissue destroyed cartilage and invaded underlying bone. Fibrous ankylosis followed, with bridging and obliteration of joints. The lesions in spondylitis resembled those of peripheral rheumatoid arthritis; minor differences included a greater tendency to hemorrhage, a greater thickening of small vessels in the form of endarteritis obliterans, and a greater tendency to bony ankylosis in spondylitis.[457]

Diagnosis. During early phases, rheumatoid (ankylosing) spondylitis may be difficult to differentiate from an atypical protruded intervertebral disc.[1157] Rheumatoid (ankylosing) spondylitis should be suspected when patients report either recurrent episodes or persistent bouts of low back pain, backache with stiffness, "catches" of pain in the back or intercostal region, and sciatic radiculitis. Limitation of flexion of the low back, "spasm" of the hamstring muscles, reduced chest expansion and characteristic roentgenographic findings serve to establish the diagnosis.[417] Generalized pains for which no cause is known and persistent cervical fibrositis in young adults should suggest the advisability of roentgenographic examinations of the sacro-iliac joints.[1609] Many patients show involvement of peripheral joints at the outset, hence spondylitis should be sought for in early cases of rheumatoid arthritis.[452]

Treatment. Therapy should be aimed at prevention or correction of postural deformity and relief of discomfort.[217] General measures, such as rest, salicylates, heat and physical therapy, were recommended.[417, 430a, 452, 1522] Regular use of postural and deep breathing exercises, as well as exercises aimed at stretching hamstring and calf muscles, was recommended.[1522]

Roentgen Therapy. This form of treatment was designated "the most effective" by some, but was also said to be difficult to evaluate. Results were not dependent upon either clinical severity or extent of involvement, but rather upon the degree of structural change and the duration of the disease.[217] "Improvement" was observed with roentgen therapy in 50 to 90% of cases.[452, 1522, 1964, 2237] Despite improvement of symptoms with roentgen therapy, serial x-rays showed progression of the disease in some instances.[417]

The technic of roentgen therapy advocated by Scott was employed with good results in one series.[1609] Others preferred a more penetrating beam. Technics of roentgen therapy employed by various writers were fairly uniform, although total dosage administered varied widely.[430a, 515, 646, 903, 1522, 1749, 2149, 2237] Transient nausea, vomiting, anorexia and malaise were bothersome side-effects of roentgen therapy; however, leukopenia was considered the only indication for terminating therapy. Somewhat smaller doses, both for individual treatments and for the total course, were recommended in the treatment of young women, to minimize possible damage to the ovaries.[1522] Others would not use x-ray therapy over the sacro-iliac or lumbar region in young women.[2149] [Certainly careful judgment should be exercised in recommending roentgen treatments to either the sacro-iliac or the lumbar regions in young women. When symptoms are mild, this therapy should be withheld. Both the patient and her family should be informed that there is some possibility of sterility.—Ed.]

Phenylbutazone. This drug was found to reduce or eliminate both pain and stiffness in as many as 80% of patients with ankylosing spondylitis. Improvement varied from slight relief to complete disappearance of symptoms, and for some patients phenylbutazone was more effective than either cortisone or x-ray therapy.[1159, 1222, 1227, 1964, 2031, 2060] While the subjective response was impressive, objective improvement was more difficult to evaluate.[2039] The result was not a cure, but the analgesic effect was marked in those patients who tolerated the drug without notable toxicity.[1223] [The toxic effects of phenylbutazone are reviewed in the section on "Rheumatoid Arthritis."—Ed.]

ACTH and Cortisone. The effectiveness and untoward complications of these agents were found to be identical in both ankylosing spondylitis and rheumatoid arthritis. With effective doses, both the symptoms and the objective manifestations of spondylitis were improved in a large percentage of the patients, but cures were not obtained.[92, 699, 903, 1008, 1215, 1703, 2030] Neither pregnenolone nor 21 acetoxypregnenolone produced results in any way comparable to those obtained with ACTH and cortisone.[290]

Surgical Correction of Deformities. The severe flexion deformity of the spine due to ankylosing spondylitis may be corrected by removing a wedge of spinous processes and laminae, fracturing the spine by extension, and immobilizing until union is again firm.[1244, 1644] This correction was carried out in more than 30 cases; there were four deaths, none directly related to the surgical procedure. In addition to an improvement in appearance, costal margins were elevated and both abdominal viscera and diaphragm were brought into better position by this procedure.[1246]

For the hip involvement in spondylitis, the results of cup arthroplasty were not as good as in osteoarthritis.[1246, 1644] Resection angulation procedures were also recommended. For marked flexion deformities of the hip or spine, a subtrochanteric osteotomy of the femur was used to restore alignment of the trunk with the lower extremity.[1466]

Course and Prognosis. The course varied greatly. The process may become quiescent at any time or progress either slowly or rapidly to calcification of the ligaments and development of the typical "bamboo spine."[217] The "preankylosing stage," marked by low back pain and pain in the chest, may last from one to six years.[643] Iritis, pleuritis and endocarditis were noted as important complications. Death was attributable to intercurrent infections in some instances.[417]

Osteoarthritis (Degenerative Joint Disease)

Osteoarthritis was defined as a "local disorder of individual diarthrodial joints. It is independent of infection and of systemic disease in general, and is brought about by abnormal mechanical conditions in conjunction with senescence, trauma or other degrading change in hyaline cartilage."[404] The name "osteoarthritis" was considered an escape from the conflict between the two equally correct though incompletely descriptive terms of "hypertrophic arthritis" and "degenerative arthritis."[404] The division into primary and secondary osteoarthritis, as outlined in previous reviews, was generally accepted. Secondary osteoarthritis may appear early in life and involve joints which are subjected to unusual wear and tear as a result of either congenital or postural abnormalities or of occupational trauma. It may also result from a single episode of severe trauma, from infections or from a vascular necrosis of underlying bone, and it often appears as a late complication of other types of arthritis.[234, 341, 909, 910, 1049, 1741, 1963]

Incidence. A diagnosis of osteoarthritis was made in approximately 30 to 40% of the patients who attended rheumatism clinics or similar departments in Great Britain.[1255] It was estimated to be present in 25 to 30% of the patients seen in the course of general office and clinic practices in the United States.[408] The incidence of osteoarthritis was determined by objective clinical and radiologic examinations in 97 miners, 47 manual laborers and 47 office workers between 40 and 50 years of age. Degenerative changes in the lumbar spine and in the knees were definitely more frequent among the miners, and there was significant correlation between symptoms and radiologic abnormalities.[1130] [This excellent study, using objective criteria and carefully selected controls, may well serve as a model for future surveys of population groups.—Ed.]

Clinical Aspects. Well recognized clinical features were again reviewed.[341, 909, 1049, 1963] The mechanism by which osteoarthritis produces pain and stiffness was not well understood. Since cartilage and bone are devoid of nerve supply, it was thought that these symptoms must be mediated through the soft tissues. Referred pain was not unusual. Possible explanations included fibrotic shortening of the joint capsule,[404, 1308] trauma to synovial and capsular tissue from bony excrescences at the articular margin, and changes in extra-articular fibrous tissue resulting from new and abnormal anatomic relationships, sometimes with associated muscle spasm; fatigue was also thought to be a factor.[349, 909, 910, 1049] Fibrositic pain appearing for the first time during the third or fourth decades may be an early manifestation of degenerative arthritis, appearing before either lipping or Heberden's nodes.[1049] Osteoarthritis may be present in an advanced stage without causing disability. As a rule, symptoms appear either when anatomic changes are marked or when osteoarthritic joints are traumatized.[910] Among patients with osteoarthritis, 88% were sensitive to changes in the weather.[2118]

The term "primary generalized osteoarthritis" was applied by Kellgren and Moore to a clinical entity which they regarded as distinct from classic degenerative joint disease and from polyarthritis of the rheumatoid type. Middle-aged women were most commonly affected. Among 196 patients with this condition, 120 showed Heberden's nodes, or arthritis of the first metacarpophalangeal joint, or both. Other metacarpophalangeal joints and the wrist joints were seldom affected. However, proximal interphalangeal joints, metatarsophalangeal joints, knees and spine were involved in one third to one-half of the cases. During the initial or acute stage the affected joints were warm, red, swollen and tender. Pain was often paroxysmal in character and had a burning or tingling quality. After several months, inflammation and pain lessened and bony outgrowths appeared about the margins of the joints. Good function was generally retained. Synovial membranes did not become thickened, and there was little tendency for joints to be seriously deformed, although lateral displacement of terminal phalanges, partial subluxation of phalanges and deformities of the first metacarpophalangeal joints were not unusual. Involvement of joints occurred in a successive manner over a long period of time. Constitutional disturbances were not observed, and laboratory tests were normal. Primary generalized osteoarthritis was thought to be a constitutional disorder, caused in all likelihood by an inherited defect.[1132] [It is difficult to be sure that this clinical entity really differs from what most workers regard as primary osteoarthritis. It may be that a special designation is justified in order to call attention to the condition.—Ed.]

A survey among college students in England showed demonstrable knee effusion in 18.3% of 213 men and 12.8% of 78 women. Among these individuals, accumulation of fluid appeared to be related to advancing age and to the size of the weight-bearing surface of the joint. Among students aged 17 to 19 years, effusions were found in 7.2%; among those aged 25 years or older, the incidence was 33.4%. In a group consisting of 48 men with small bones and greater weight, the incidence of effusions was 31.3% whereas among a group of 74 men with larger bones, the incidence of effusions was only 14.9%. These findings suggested that effusion might be related to some mechanical factors, and degenerative changes were considered to be the most likely cause. In many instances small effusions occurred without symptoms and might easily have been overlooked.[1606] [The method of examination is described in detail. The author commented: "The discovery of so many effusions came as a surprise to the author and also to others who, hearing of it for the first time, were inclined to doubt the authenticity, or more cautiously to inquire for details of the method of examination."—Exactly our reaction. More convincing evidence that the findings were actually due to effusion would be obtained by aspiration and examination of the joint fluid.—Ed.]

Pathology. Well recognized changes associated with osteoarthritis included initial softening and fibrillation of superficial layers of articular cartilage, followed by condensation of subchondral bone, marginal overgrowth of both cartilage and bone, and eventual disorganization of affected joints.[548, 910, 1017, 1125, 1245] Kellgren suggested the initial lesion of osteoarthritis to be a decrease in the polysaccharide component of cartilage, leading to a breaking up and disintegration of unsupported collagen fibrils in consequence of continued use.[1125] Analysis of fibrillar cartilage removed from different areas in five osteoarthritic knees showed a greater decrease in content of chondroitin sulfate than of collagen.[1399] [This change may be more closely related to the aging process.—Ed.] Small fragments of bone and cartilage believed to originate from the degenerated articular surface were found beneath the synovial surface in 23 of 25 cases of osteoarthritis of the hip. Fibrosis of the synovial membrane and capsule was associated with phagocytosis of these cartilage fragments and resulted in capsular shortening.[1308]

In an important study of 146 femoral heads, utilizing vascular injection com-

bined with radiographic, transparency and special histologic technics for demonstrating blood vessels within bone, Harrison, Schajowicz and Trueta demonstrated that osteophyte formation began as a reaction of the juxtachondral blood vessels to degeneration of the articular cartilage. The increased vascularization may come from adjacent subsynovial tissues or subchondral vessels. Hyperemia followed by growth of vessels led to cartilage invasion and bone changes. Vigorous and persistent attempts at cartilage repair led to osteophyte formation as well as to hypervascularity of bone with weakening of trabeculae and collapse of bone. This provoked further attempts at repair and, in turn, further destruction. "What is so damaging in osteoarthritis seems to be not the degeneration of cartilage, but the vigorous and persistent attempts at repair." [899] These workers also found "no evidence in support of the common belief that the circulation within the femoral head decreases quantitatively with advancing age." [2143] [This impressive study should help to dismiss the lingering hypothesis that vascular insufficiency is an important factor in the pathogenesis of osteoarthritis.—Ed.] Bone cysts were attributed to fibrous replacement of necrotic bone and marrow,[899] and to intrusion of synovial fluid under pressure into the substance of the bone.[1234] In some cases of degenerative hip disease secondary to rheumatoid or infectious arthritis, bone softening permitted the femoral head to intrude deep into the acetabulum and pelvis.[1017] [Otto pelvis.—Ed.]

Etiology and Pathogenesis. Osteoarthritis does not have a single cause. Primary osteoarthritis was generally attributed to "wear and tear." The speed of this process was thought to depend upon unknown factors of cartilage metabolism which determine resistance to stress. Secondary osteoarthritis was attributed to injuries and was believed to follow in the wake of other diseases of joints, including rheumatoid arthritis and gout, also certain congenital and mechanical derangements of joints.[910, 1037, 1125]

Genetic studies on Heberden's nodes were summarized as indicating that these lesions appear in accordance with an inherited pattern which is dominant in women and recessive in men, with penetrance dependent on age.[2008, 2010] Another case report described unilateral Heberden's nodes in the unaffected hand after hemiplegia.[2272] A relationship between Heberden's nodes and cervical osteoarthritis was suggested by a study in which the incidence of both conditions increased with age at similar rates. Compression of nerve trunks in intervertebral canals, with resulting degeneration, was believed to be the cause of Heberden's nodes. Some patients with unilateral Heberden's nodes had unilateral cervical osteoarthritis, but Heberden's nodes were not present in many of the patients with cervical osteoarthritis.[1631] [The diagnosis of cervicular osteoarthritis was made by x-rays only. There was no evidence that the findings reported do not represent merely expected coincidence rather than cause and effect.—Ed.] Angiograms of the hands in five patients demonstrated arterial insufficiency associated with osteoarthritis, leading to speculation that cartilage atrophy resulted from ischemia.[1259] [No statistical data were given and no control studies reported. The author did not prove this thesis.—Ed.] Personality factors were evaluated in 20 patients with osteoarthritis, and the hypothesis was offered that the symptomatology accomplished a limitation of aggression in a psychosocially maladjusted individual.[1291] [Apparently psychosocial maladjustment and osteoarthritis are among the most common disorders of mankind. It would be remarkable if they were not often found together in the same individual. Such association is no proof of cause and effect.—Ed.]

In continuation of their studies of the influence of diet and hormones on skeletal growth, articular aging and degenerative joint disease of mice, the Silberbergs demonstrated a protective effect from a high protein intake and an acceleration of skeletal

aging by a high fat or high calorie diet.[1920, 1921, 1922, 1923] Since the effects of a high fat diet were less marked in females, and ovariectomy accentuated this dietary effect on degenerative skeletal changes, it appeared that estrogens may be protective.[1919] [A closely inbred strain (C 57) of black mice was used in these experiments. These mice show a fast rate of skeletal growth and aging.—Ed.] Examination of 35 hamsters did not show complete correlation of osteoarthritis of the knee joint with advanced changes of aging elsewhere in the body.[1924]

Mechanical factors contributing to the development of secondary osteoarthritis of the hip and knee may not be obvious. Dysplasia or poor formation of the acetabulum, with or without subluxation of the femoral head, was believed to be responsible in approximately 25% of the cases of osteoarthritis of the hip.[1017] Osteoarthritis may affect the knee during early adult years when either stability or mobility has been affected by injuries,[1868] or progressive changes may be initiated by degeneration of the semilunar cartilages.[1202]

Laboratory Data. No new diagnostic laboratory procedures were reported. Erythrocyte sedimentation rates were less than 20 mm. per hour (Westergren method) in 66 of 112 patients with primary generalized osteoarthritis, between 20 and 40 mm. in 38 patients, and 40 mm. or more in eight patients. In contrast, all of 20 patients with mono-articular degenerative arthritis showed sedimentation rates of less than 20 mm. per hour.[1132] The sensitized sheep cell agglutination test was positive in only eight (3.2%) of 249 patients with osteoarthritis.[1125]

Liver function appeared normal in eight patients with osteoarthritis.[68] No significant abnormalities were noted in the plasma creatine concentration or the level of creatinuria in either rheumatoid arthritis or osteoarthritis.[497]

Roentgen Studies. During late stages of primary generalized osteoarthritis, roentgen findings were similar to those seen in osteoarthritis. A combination of Heberden's nodes and arthritis of the first metacarpophalangeal joint was a characteristic finding. The intervertebral discs remained relatively unaffected, and vertebral osteophytes were unusual. However, articular facets and neural arches (including spinous processes) became enormously enlarged and sclerosed. When the knees were involved, joint spaces were narrowed, and rounded "molten wax" bony outgrowths appeared at articular margins, rather than the sharp-pointed osteophytes characteristic of the more usual osteoarthritis." [1132]

Early idiopathic Heberden's nodes were recognized by means of lateral radiograms, which showed small islands of bone in extensor tendons adjacent to the distal phalanges. In traumatic arthritis of the terminal interphalangeal joint a heavy bone buttress extended dorsally from the proximal end of the distal phalanx.[2010] The characteristic findings of malum coxae senilis were again described in detail.[1017, 1245]

A study of 390 roentgenograms of the hips showed normal findings in 233; 67 with evidence of osteoarthritis had no symptoms of hip-joint disease, whereas 90 presented both clinical and roentgen evidence of osteoarthritis. The depth of the acetabula of asymptomatic osteoarthritic patients showed a normal distribution curve; in contrast, a majority of patients with both clinical and radiologic signs of osteoarthritis showed relatively shallow acetabula.[1758]

Treatment. Avoidance of overuse or injury to the affected joints, weight reduction,[1309] analgesics, reassurance, education,[2195] physical therapy and exer-

cises,[97, 1868] and well directed efforts at rehabilitation[473] again constituted the basic treatment program.[342, 909, 910, 1049, 1204]

Phenylbutazone. This drug was effective in relieving pain, at least to some degree, in 65 to 80% of osteoarthritis patients. This drug did not cure the condition; it had to be given continuously, and exerted no influence on the course of degenerative joint disease.[462, 1222, 1223, 1814, 2031, 2060] In the largest series—166 patients with osteoarthritis—major symptomatic improvement was obtained in 51%, but 30% were unimproved or worse.[1227] In malum coxae senilis, one report noted great or complete relief of pain in 11 of 16 patients;[482] others were less enthusiastic, although in some patients the analgesia was better than that achieved with salicylates.[1223] [The toxic effects of phenylbutazone are discussed under the section on "Treatment of Rheumatoid Arthritis." The dangers and precautions noted there apply equally to the use of this drug in osteoarthritis. Its use should be restricted to those patients with severe pain which cannot be controlled by safer analgesic agents.—Ed.]

Corticotropin and Corticosteroids. No consistent effect of these hormones was reported, aside from temporary relief of pain during their administration. Euphoria may have been as important as analgesia here. Excessive use of osteoarthritic joints sometimes resulted in rapid progression of primary osteoarthritis, or in a rapid development and progression of osteoarthritis secondary to other disease of joints. While sometimes painful osteoarthritis of the hip responded with temporary relief, no permanent benefits were observed.[234, 280, 548, 699, 909, 1485, 1703, 2030, 2032] ACTH, cortisone and hydrocortisone supposedly exerted analgesic and anti-inflammatory effects when administered during traction following manipulations or after surgical procedures.[672, 2032]

Intra-articular injection of hydrocortisone was recommended for patients with only one or very few painful osteoarthritic joints. Relief from pain lasting for periods of two to 10 weeks was reported. Subsequent to this local therapy, in some instances excessive use of osteoarthritic joints resulted in rapid deterioration.[495, 985, 1715, 1827, 2051] [The use of intra-articular hydrocortisone is most likely to benefit osteoarthritis of the knee. Results in degenerative disease of the hip joint are less satisfactory.—Ed.]

Other Special Measures. Injections into the joint of a variety of substances were reported to have provided symptomatic relief. These included phenylbutazone,[966] procaine,[166, 2136] potassium acid phosphate[2197, 2227] and osmic acid.[2174] Similar results were said to result from injection of Priscoline into femoral arteries,[496] and of para-aminosalicylic acid into periarticular tissue.[278] [These reports are notable for lack of objective data and absence of control observations.—Ed.] In a carefully controlled study, 189 osteoarthritic joints were injected with alkaline procaine solutions, lactic acid solutions or saline solutions; some were needled without injection. Some patients in each group reportedly improved. However, the differences between those who received the procaine or lactic acid solutions and those who received saline or were merely needled were not statistically significant.[514] [This report rings true. The controlled tests were carefully reported.—Ed.]

Cobra venom administered in much larger doses than previously used was reportedly "beneficial."[965] Massive doses of vitamin B_{12},[881] pregnenolone,[1417] intravenous and oral procaine,[1182, 2136] intravenous mephenesin,[1437] and oral mephenesin together with glutamic acid,[941] were reportedly effective in a "high percentage of patients with osteoarthritis." [These papers have done little to clarify the problems of

therapy for osteoarthritis. Observations on controls, establishment of recognizable objective criteria and avoidance of flamboyant claims are highly recommended for all physicians seeking to evaluate therapeutic measures in this field.—Ed.] The combination of aspirin with calcium succinate was found to be no more effective than aspirin alone.[445, 2129] [This combination is a proprietary preparation widely advertised under the name of "Dolcin."—Ed.]

Physical Therapy. The value of physical therapy for osteoarthritis was again emphasized.[329, 909, 910, 1037, 1309, 1868] Ultrasonic energy was reported as beneficial.[1857, 1988]

Surgical Treatment. Arthrodesis, debridement and nylon arthroplasties were again recommended for osteoarthritis of the knees.[1205] Good results were obtained in eight of 10 osteoarthritic knees after nylon arthroplasty.[1207] Patellectomies, synovectomies and debridements were also championed for "severely affected knees which still have a reasonable range of motion and adequate ligamentous stability, provided the patient is willing to cooperate in a painful prolonged aftertreatment."[1053] Of 26 patients treated by complete patellectomy, only two were not benefited; results were excellent in 10.[736] [It will require careful and objective observation to evaluate how well results from these surgical procedures are sustained.—Ed.]

Numerous publications on surgical treatment of osteoarthritis of the hip appeared. Among procedures described were manipulations under anesthesia, neurectomy, acetabuloplasty, capsulectomy and debridement, osteotomy, arthrodesis, arthroplasty, and replacement prosthesis of the femoral head.[349, 406, 412, 638, 892, 1203, 1245, 1480, 1679, 1741, 1742, 2051, 2112]

Such procedures were not recommended unless severe deformities are present or unless pain is especially severe. "Surgical therapy should not be undertaken until conservative management has failed, . . . and the more simple procedure should be used first."[1739a]

Fusion operations sometimes failed to produce sound union between the articular surfaces; 17% of 128 patients failed to obtain an arthrodesis after the first attempt.[2052] Even when successful, this procedure was often followed by pain in the knee or lumbosacral area.[1464, 2052] Operations were described for replacement of the femoral head by means of 40 types of prostheses.[277, 753, 1203, 1549, 2112] In a one to five year follow-up of Vitallium cup arthroplasty in 63 patients, it was found that patients valued relief of pain more than the improvement of motion.[2052] Convalescence from femoral head replacement was easier and early results were considered good, but few patients had been followed more than one or two years.[1206, 2052] Muscle transplant to the femoral neck, to correct a postulated ischemia responsible for pain, gave poor results.[1456]

Osteoarthritic Spondylitis

Spinal osteoarthritis is seen commonly among older men, especially in those who have done heavy work. Patients with prominent changes in roentgenograms may have few or no symptoms. Therefore, asymptomatic osteoarthritic spondylitis should arouse little concern when encountered during routine examinations. Degeneration of discs with subsequent narrowing of intervertebral spaces and over-riding of apophyseal joints may lead to spinal osteoarthritis. Abnormal pressure may cause osteophytes to appear on the margins of vertebral bodies, and abnormal pull on vertebral periosteum may also cause osteophyte formation. Spurs located on the posterior aspects of vertebral bodies often cause compression of nerve roots within intervertebral foramina. Pain associ-

ated with spinal osteoarthritis may result from articular lesions, nerve-root compression, chronic ligamentous strains or from muscle spasm.[378, 623, 624, 981, 1849]

A postmortem study of 41 sacro-iliac joints from persons over 50 years of age showed changes with age comparable to those seen in other joints.[1351] A comparison of roentgenograms of the spine taken of persons in Saskatchewan, Canada, with similar films from Bristol, England, showed that spinal osteoarthritis was more frequent in Canada.[164] [No explanation was offered.—Ed.] An anatomic study of the second cervical vertebra revealed many variations in size, shape and angle of inclination of the articulating facets. These asymmetric joints were predisposed to mechanical instability, ligamentous strains and irritation of capsular ligaments.[1598] A superior lateral lip, projecting posteriorly to form an anterior wall for the intervertebral foramina, was found to be characteristic of the third, fourth, fifth and sixth cervical vertebral bodies.[250]

Clinical Features. The usual syndrome of pain and stiffness of the neck, with gradual progressive limitation of motion of the cervical spine, is well known. Cervical osteoarthritis was said to include (1) lesions of discs and associated reaction in bone; (2) exostoses, including lippings and spiculations, and (3) deforming changes of small intervertebral joints.[1340] Narrowing of the intervertebral foramina with compression of nerve roots causing radicular pain to the upper extremities, head, neck and shoulder girdle was also recognized. These syndromes have been termed brachial neuralgia, pseudoangina, facial and occipital neuralgia and sometimes herniated cervical discs.[624, 1597, 1849] Pain localized to the distribution of the third cervical segment (the scalp over the postauricular, occipital and posterior parietal region) constituted 20 of 186 investigated cases of cervical radicular pain.[1598]

The association of cervical osteoarthritis with disorders of the spinal cord was again emphasized. The clinical picture duplicated that seen with a median protrusion of a cervical disc, and in fact was attributed to posterior marginal osteophyte formation resulting from abnormal pull by a bulging annulus, often associated with intervertebral disc degeneration. The causative lesions were usually visualized by myelography using lateral and anterior-posterior projections.[257, 623, 624, 1256, 1995] Postmortem examination in one such case showed ridges overlying the disc spaces which expanded laterally into two osteophytic protrusions. These ridges were made up of disc protrusions covered by bony outgrowths from edges of adjacent vertebrae. The spinal cord was held firmly against the bone and showed indentations from pressure of the ridges.[139]

In the lumbar spine, single or multiple osteophytic ridges similar to those in the cervical spine were found. These sometimes constricted the spinal canal and compressed the cauda equina, producing neurologic changes.[624] Normal spinal curves were exaggerated, and both lateral motion and rotation were restricted in primary generalized osteoarthritis of the spine. Flexion and extension were usually well maintained, even in those patients having severe changes affecting articular facets.[1132]

X-ray Findings. The usual findings were reviewed.[249, 378, 866, 1340, 2131] Constricted intervertebral foramina and marginal osteophytes protruding posteriorly into the spinal canal were visualized by means of oblique and lateral views. Conventional views were often inconclusive because of incomplete calcification of offending osteophytes. A correlation of roentgenograms with anatomic findings in spinal osteoarthritis showed nerve root compression could be caused by displacement of intervertebral joints from below upward and forward into the foramen. This condition resulted from intervertebral disc degeneration. Sliding of an upper vertebral body

either back from the vertebral margin or forward from the apophyseal joint margins further narrowed the foramen and reduced the reserve space about the nerve root.[866] "Eagle beak" or "goose bill" shaped spurs adjacent to narrowed intervertebral spaces were designated as "discogenic" spurs; they were thought to result from anterior herniation of intervertebral discs.[378]

Treatment. Osteoarthritis of the spine is incurable in the sense that the basic damage cannot be repaired, and spurs cannot be removed except surgically. Elimination or mitigation of those stresses which accelerate normal wear and tear was considered important for such patients.[909] Much could be done to relieve persons with cervical osteoarthritis who were treated early by means of traction, local heat and analgesics. Surgical procedures were reserved for those showing signs of damage to the spinal cord.[624] Roentgen therapy was ineffective in correcting pathologic changes, but was said to alleviate pain in some patients.[1340] [Little new has been added to the treatment of osteoarthritis of the spine. This does not mean that little can be done for patients who will coöperate in carefully planned programs, which include the judicious use of analgesics and physical therapy and the elimination of aggravating mechanical factors. The principles of such a program are outlined in previous Reviews.—Ed.]

Backache and Sciatica

Many writers stated that practically all backaches are due to pathologic lesions in intervertebral discs.[309, 1158, 1915] Others attributed backache to a variety of diseases of the spine and to many extraspinal diseases.[1566, 1567, 2265, 2301, 2302] General aspects of the symptoms, physical findings and x-ray findings in backache were covered in a number of papers.[309, 871, 1103, 1410, 1567, 1864, 2120, 2301]

Several causes of backache mentioned in previous reviews were disappearing from the literature, or their importance was minimized. Most writers believed that diagnoses of sacro-iliac strain and sprains are out of fashion and that these conditions are either decidedly rare or nonexistent.[113, 323, 734, 1567, 1785, 1915, 1974, 2003, 2120] Hypertrophy of the ligamentum flavum was not believed to be of clinical significance.[871, 1915, 2242] Disc disease rather than spasm of the levator ani, coccygeus and piriformis muscles was held responsible for backache associated with unilateral gluteal pain.[1153, 1264, 1915] Some patients who complained of backache and stiffness and in whom roentgen studies were negative were considered to have fibrositis.[229, 734] [Backache due to fibrositis and to subfascial fatty herniations is reviewed under the heading of "Non-Articular Rheumatism."—Ed.] Assumption of the erect posture was believed to have placed a great strain on the lumbosacral juncture. When man is in the erect position this joint is fixed in extension, and pressure falls on the posterior margin of the annulus fibrosus. Symptoms heretofore attributed to lumbosacral strains may in fact be due to this pressure on the annulus. This pressure may eventually cause degeneration of discs and protrusion of the nucleus, with the ensuing development of osteoarthritic changes.[1625, 2176]

One study compared the roentgenographic findings in the lumbosacral region in 100 persons without backache who were 40 years of age or older with those in 100 persons with low backache regardless of age. Few differences were noted. Congenital anomalies were equally frequent in the two groups. Degenerative changes were slightly more frequent in patients with backache. In both groups, facets in the

lumbosacral regions faced either obliquely or anteroposteriorly. Interspaces between the fifth lumbar and first sacral segments were equally wide in both.[2000]

Postural Backache. Faulty posture, with exaggeration of lumbar lordosis, usually associated with a tilted pelvis, an ovoid abdomen and dorsal kyphosis, was again considered to be a frequent cause of low back pain. The basis for this condition was believed to be established during childhood and adolescence. Symptoms became bothersome during middle life or during pregnancy.[1884] Weakness of abdominal muscles incident either to sedentary habits of middle life or to obesity may result in hyperextension of the lower part of the back and increase in the angle at the lumbosacral joint. The consequence is strain on ligamentous structures.[734, 2120, 2178] Among individuals with poor posture, joint structures may be at or near the normal limits of motion. If this limit is exceeded, ligamentous strain with pain results and the back is said to be "decompensated." Trauma, acute illness, psychic factors, pregnancy, ill health, faulty feet, obesity and fatigue were all factors which may cause strains and decompensation. More than one factor was generally responsible.[1611] Some distinctive characteristics of pain caused by lumbosacral strain were its location in the lumbosacral region, its usual appearance late in the day after periods of activity and standing, and its relief by flexing the lower lumbar spine. Roentgenograms generally showed a "horizontal" sacrum with an abnormally acute angle between the lower lumbar and the sacral segments. Overriding, arthritic changes and congenital deformities were often present.[871, 1611, 1884, 2178]

Rest was advised for severe pain.[2178] Also helpful were exercises designed to strengthen gluteal and abdominal muscles and to improve "sway back."[734, 1200, 1611, 1884, 2120, 2178] Persons suffering from this condition should avoid sleeping on the abdomen and should place pillows under the knees when sleeping on the back in order to minimize morning backache. Avoidance of high heeled shoes, care in lifting, and standing with one foot on a step when working at a bench were recommended.[1050]

Industrial Backache. Low back pain constituted a major problem in industrial medicine; successful management demanded first of all an accurate and exact diagnosis.[113, 1410] In young men, industrial backache was most often caused by either congenital weakness, rheumatoid spondylitis or postural defects. In middle years, protruding discs were more often responsible, and in older persons the cause was generally osteoarthritis. Both osteoarthritis and degeneration of discs were encountered with unusual frequency and at an earlier age among persons engaged in heavy work.[113, 2120] No causal relationship was found between industrial injuries and occurrence of the disc syndrome in one investigation involving 332 patients. This syndrome occurred much more frequently among persons who were not accustomed to heavy work, and generally followed some sudden exertion in connection with movements such as lifting, bending, twisting, or falling on the back.[1233]

Results of surgical treatment for backaches incurred in industry were generally disappointing. In one center, only one industrial worker in three returned to his former occupation after surgery.[1410] In another study of 200 patients who underwent operations on intervertebral discs following industrial accidents, no protruding discs were found in 17.5%. Among patients in whom disc herniations were found, fully a third failed to return to work within two to five years. Among those without protruding discs, 47% failed to return to work.[19] In another group, 83% of nonindustrial workers returned to work, whereas only 70% of industrial workers returned to their jobs.[256]

Congenital Anomalies. As in previous years, these were thought to engender a poor mechanical condition of the back, producing pain which usually appeared in

the second or third decades.[1567, 1625, 1864] But Splithoff found congenital anomalies not to be more frequent in patients with backache than in subjects without backache.[2000] Accessory sacro-iliac joints between the ilium and sacrum may become arthritic and be responsible for symptoms.[867] In a roentgenographic analysis, degenerative changes in discs were present in nine of 10 cases of lumbarization of the sacral segments, and in 15 of 30 cases with sacralization of the lumbar vertebrae. In such instances the damaged discs were held responsible for clinical symptoms.[917] Roentgenographic survey of 1,500 male applicants for railroading jobs showed that 675 (45%) had one or more spinal anomalies. Spina bifida was the most frequent lesion, occurring in 299 individuals (20%). Transitional segments were found in 71 individuals (4.7%) and spondylolysis in 44 (2.9%), 23 of whom had spondylolisthesis.[393]

Spondylolisthesis. Spondylolisthesis was believed to cause an unstable condition in the lower part of the back, resulting in pain attributed to stresses and strains exerted on the ligaments. Symptoms resembled those encountered in connection with postural backache, being relieved by lying down and by flexion of the lumbar region. Degeneration of the discs accompanied by posterior protrusion of the nucleus was a frequent occurrence, but significant damage to nerve roots was not often a complication.[876, 2120] Nerve root pressure with radiating sciatic pain in spondylolisthesis and spondylolysis may be produced by several mechanisms.[112] A majority of patients with spondylolisthesis were relieved by medical measures and did not require operations. When there was protrusion of a nucleus, spinal fusion was often needed in addition to removal of the protruding disc.[309]

The etiology of spondylolisthesis remained in dispute. Majority opinion favored a congenital origin, but trauma, particularly at birth or during infancy, also had supporters.[1501] Transition from spondylolysis to spondylolisthesis was carefully documented in a single case.[1165] [Few such documented cases have been reported.—Ed.]

Spondylolisthesis without defects in the neural arch, "pseudospondylolisthesis," usually affected the fourth lumbar vertebra. The essential lesion was an increase in the angle between the inferior facets and the pedicles, allowing subluxation to take place at the inferior joints. Symptoms resulting from this condition were those of nerve root compression.[1358] Reverse spondylolisthesis, usually with posterior displacement of the fifth lumbar body on the sacrum, most often represented a mechanical consequence of disc degeneration.[1852, 2120]

Diseased Facets. Damage to facets secondary to degeneration of discs was regarded as a fairly frequent cause of backache, and may account for persistence of symptoms after removal of a herniated disc. Narrowing of disc spaces may be associated with subluxation of the facets.[1625] It was thought that ligamentous structures supporting the facets at times might fail to maintain normal joint stability; the resultant separation of apophyseal joint surfaces could account for episodes of acute low back pain which occur suddenly with activities such as attempting to straighten up after picking up an object.[1198]

Spinal Osteochondritis (Adolescent Kyphosis; Juvenile Epiphysitis; Scheuermann's Disease). The condition was observed in young individuals prior to completion of spinal ossification, and was especially frequent in persons who bear heavy loads. Characteristically there was marked kyphosis at the lower thoracic region, with roentgenographic findings of irregularities about the margins of one or more vertebrae, anterior wedging of vertebral bodies and wavelike irregularities involving both superior and inferior surfaces of vertebal bodies. Changes may be localized to the area of the thoracolumbar junction. Twice as many males as females were affected.[869, 2202] Incidence of spinal osteochondritis among persons rejected for service in the Danish army was 32,000 among 481,000 rejectees. The incidence was eight times as high among persons from rural areas as among city dwellers. Inasmuch as boys on farms often do heavy physical work before their tenth year, occupational

trauma appeared to be implicated. Only one among 24 persons with this condition did not engage in heavy physical work. This study showed a tendency towards a familial or "pseudohereditary" incidence determined by the common factor of heavy work, but several examples of genuine inheritance were reported. Incidence of spinal osteochondritis was 8.5% among men of conscription age in Sweden.[2202]

The cause of osteochondritis remained unknown. No evidence has been produced to link hormonal or vascular disturbances, dietary deficiency or rickets to this condition. The erect posture may be a factor, inasmuch as man is the only species affected.[869, 2202]

Osteitis Condensans Ilii. Osteitis condensans ilii was noted in 17 (2.2%) of 760 cases in which the lumbosacral spine was examined roentgenographically. Roentgenograms showed rather sharply defined unilateral or bilateral homogeneous areas of osteosclerosis of the ilium close to the sacro-iliac joints. The adjacent joint was not involved; joint surfaces were smooth, in contrast to involvement by tuberculosis, infection or rheumatoid spondylitis.[756] Characteristically, 95% of patients were women, most of whom had borne children, but difficult labor, puerperal complications and numbers of pregnancies did not appear to be contributing factors.[2153] One series of 28 cases was composed of two men and 26 women; of the latter, six had never been pregnant.[1035] Some doubted that this condition per se is ever a cause of backache.[756]

In addition to six previously reported cases, 30 new cases were described in which osteitis condensans ilii was associated with kyphosis dorsalis juvenilis (Scheuermann's disease). Thus osteitis condensans ilii was thought to be a direct result of juvenile epiphysitis affecting the sacro-iliac joints. The fact that this condition was rarely observed among older individuals suggested that the process may be reversible.[2153]

Osteoporosis. Patients with osteoporosis generally complained of a dull backache and fatigue, often of several years' duration. Minor injuries and accidents precipitated episodes of severe pain. In some instances pain was referred either upwards or downwards along the spine, along the ribs, into the anterior portion of the chest or to the epigastrium. The symptoms generally were completely relieved by lying down. As the condition continued there was a progressive tendency towards kyphosis in the region of the dorsal spine, associated with lordosis of the cervical spine. Some patients remained remarkably well and had few symptoms. In some, tenderness to pressure over the cervical spinous processes was the only notable finding.[908] Roentgenograms showed decreased density of vertebral bodies (most marked in the lumbar and dorsal regions), ballooning of discs producing biconcave "codfish" vertebrae, and compression fractures.[430, 908] Narrowings and irregularities of contour frequently affected the disc spaces adjoining fractured vertebrae. It was difficult to assess the severity of osteoporosis, inasmuch as no satisfactory method of measurement has been devised. Asymptomatic compression fractures involving one or more vertebrae were found in 35 (26%) of 136 persons ranging in age from 63 to 95 years. The twelfth dorsal and the first lumbar vertebrae were most often affected. Osteoporosis with degenerative changes was usually present.[746]

This condition was attributed primarily to decreased activity of osteoblasts, with resulting decreased production of osteoid or organic matrix. Controlling factors for osteoblastic activity included (1) mechanical stimulation by activities such as weight-bearing, (2) certain steroid hormones, including androgens and estrogens, (3) availability of protein, and (4) the conditions which determine direction of nitrogen balance.[430] Levels of serum calcium and phosphorus were usually normal.[908] The distinction between postmenopausal and senile osteoporosis remained obscure.[746, 908, 1854] Senescent human vertebrae not subject to any abnormal endocrine influence showed osteoporosis or atrophy, osteophytes located at the peripheral margins and

localized regions of avascular necrosis or infarcts within the spongy portion of the bone. Collapse of the vertebrae was not observed in this group.[180] Nutritional factors were emphasized in a study of 33 older individuals whose calcium intake ranged from 200 to 1100 mg. daily. There was good correlation between the presence of osteoporosis of the spine and a tendency to choose diets low in both calcium and phosphorus.[2178] [This type of post hoc reasoning may very well lead to wrong conclusions. The cause of senile osteoporosis remains obscure.—Ed.] Another study called attention to the coexistence of osteoporosis of the spine and pelvis with an unusual condition of thinning of the parietal bones of the skull, long recognized by anthropologists and pathologists.[622]

Good results in treatment of osteoporosis were claimed for testosterone propionate given with estradiol benzoate or diethylstilbestrol.[908, 1049, 1854] However, there were no convincing reports of increased bone density following estrogen therapy.[908, 1896] [It is difficult to assess the value of treatment with sex hormones. Pain is often relieved in patients with uncomplicated osteoporosis.—Ed.] Testosterone may have undesirable effects and should not be prescribed in a haphazard fashion. In general, prolonged immobilization is contraindicated for osteoporotic patients.[908]

Malignant Disease of the Spine. Persistent severe backache which cannot be relieved by ordinary measures should arouse the suspicion of malignancy. Several writers called attention to patients in whom metastatic neoplasms caused symptoms resembling protruded discs.[786, 1567, 2301, 2302] Sarcoma, Ewing's tumor and leukemia also caused destructive lesions in vertebrae.[1567] Although the lumbar spine was found to be the site of metastases in 40% of persons dying with malignant disease, metastatic lesions were detected in roentgenograms in fewer than half of the cases.[1752] Primary malignancies originating in the lungs, greater curvature of the stomach, body of the pancreas and prostate gland often may be "silent," causing no symptoms until metastases develop in the spine. Backache may also be an early symptom in Hodgkin's disease and multiple myeloma.[824, 2301, 2302] [Some patients with multiple myeloma show only osteoporosis of the spine, rather than the classic osteolytic lesions. Marrow aspiration may be necessary to distinguish such cases from senile osteoporosis.—Ed.]

Urologic Lesions. Urologic lesions designated as causes of backache included infections, calculi and malignancies of the prostate, seminal vesiculitis, urethral and ureteral strictures, and infections, calculi and malignancies of the kidneys.[1a, 1551] Diseases of the lower portions of the genitourinary tract were sometimes associated with pains localized in the thighs. Perinephritic abscesses and carbuncle of the kidneys occasionally cause backache and spasms of lumbar muscles.[1a, 1567] In women, disease of the urethra may cause back pain similar in character to that observed in men with diseases of the prostate gland. Carcinoma of the prostate may cause persisting, severe backache that is aggravated by activity.[2238]

Gynecologic Lesions. Neoplasms originating in the ovaries and uterus, uterine displacements and other diseases of pelvic organs in women sometimes caused backaches.[2301, 2302] During the latter months of pregnancy some women had backache caused by muscle strain.[1567] Among 200 women who complained of backache, gynecologic abnormalities were present in approximately half. But 58% presented roentgen abnormalities in the lumbosacral spine capable of causing the symptoms. In 27% of the entire group, gynecologic abnormalities were found in patients with normal x-rays of the spine. In 15%, neither gynecologic nor roentgenographically visible abnormalities were observed.[2165]

Gastrointestinal Lesions. Peptic ulcers should be included among the causes of backache. Also responsible in some instances were malignancies of the stomach, retrocecal appendicitis and diseases of the pancreas and gall-bladder.[134, 1567, 1952] Pains resulting from lesions which cause abnormal tensions on muscular walls may be referred to the back. Lesions which involve either the parietal peritoneum or the posterior peritoneal structures may also cause backache. Tenderness of spinal muscles and spasms were observed in such patients. Penetration of peptic ulcer into the pancreas, carcinoma of the pancreas, and even peptic ulcer which did not involve the pancreas were occasionally responsible for backache.[134]

Psychogenic Backache. General aspects of psychogenic rheumatism are covered elsewhere in this review. It was not unusual to encounter patients in whom psychosomatic overlay was a complication of organic ailments of the back.[25] "Fear, anxiety and preoccupation are potent in augmenting back pain. Good patient-physician relationship allays fear and decreases pain. The inept physician can multiply fears and may contribute to the production of an ineradicable psychic overlay. The psychosomatic problems of low-back pain are fascinating and poorly understood. Neuroses including hysteria and depressions may translate loss of economic security into a powerful augmentation of the pain from a relatively trivial muscle strain." [112]

A number of writers described neuroses, psychoses, chronic emotional disturbances and malingering as causes of backache.[430, 472, 688, 1567] Some stated that generalized and sustained hyperfunction of skeletal muscle as part of a reaction to a threatening situation may cause pain in the back and neck, and in the extremities.[1004] Among 122 soldiers with backache studied in an Army hospital, only 38.5% had evidence of organic disease; 54.2% presented evidence from the history and course of the ailment suggesting a psychogenic basis, and 7.3% were unclassified. Of 49 patients with psychogenic backache, the psychiatric diagnosis was hysteria in 34 and anxiety neurosis in 15.[536]

Backache and Sciatica from Diseased Intervertebral Discs

Disc protrusion was designated as the most common cause of persistent low back pain and sciatica. Many patients with low back pain and sciatica recovered without operation before the disc syndrome was well understood. A majority of the patients with this condition still recover with conservative measures if given sufficient time.[1158]

Anatomy and Physiology. Several excellent reviews included detailed anatomic descriptions of intervertebral discs.[378, 819, 972, 1622, 1915, 2053] Each intervertebral disc consists of three distinct parts, the cartilaginous plates, the annulus fibrosus, and the nucleus pulposus. The plates of hyaline cartilage are cemented by thin layers of calcified cartilage to the intervertebral surfaces of adjoining vertebral bodies. The annulus fibrosus binds the vertebral body to the cartilage plate and also to the bony epiphyseal ring; it constitutes a fibrous envelope surrounding the nucleus pulposus. The nucleus pulposus does not lie free in the disc but is formed by fine interlacing fibers extending from the fibrocartilaginous envelope, embedded in a gelatinous matrix of mucoid material and interspersed with cartilage cells. The nucleus consists of moderately tough, highly plastic, semiliquid material resembling nontendinous moist fascia or wet blotting paper. It is incompressible, behaves like fluid, and has been compared to a shock ab-

sorber. The surrounding annulus, composed of concentric rings of tissue, is compressible and elastic. Thus the nucleus and annulus together function as a hydraulic ball bearing. Water content of the disc decreases with age. Elasticity is diminished during the fourth decade of life, as the nucleus becomes tougher and less fluid.[819, 1786] Studies of dry weight and sulfur content of nuclei pulposi at various ages showed alteration of the ratio between collagen and polysaccharide present. The protein material increased and the carbohydrate fraction remained the same, while the water content decreased as the age increased.[971]

The intercellular matrix of the nucleus pulposus was shown to consist of collagen fibrils, a polysaccharide component, a protein component attached to the polysaccharide, and water. The water content was 83%. By electron microscopy the intercellular matrix appeared to be a "three-dimensional lattice gel system with a regular molecular pattern." Poorly differentiated collagen fibrils formed a dense network, and the surfaces of these fibrils were coated with a polysaccharide-protein complex which rendered them hydrophilic.[2088, 2090] Diffusion constants in fresh nucleus pulposus were of the same order as in gelatin gels of identical water content.[1620] During the third decade of life progressive changes of a "degenerative" nature affected both cells and matrix of the nucleus pulposus. A decrease in the number of cells paralleled a patchy loss of mucoid material. Large collagen fibril bundles appeared, while water content diminished. The result was a notable alteration of the regular lattice gel pattern associated with earlier life and hence loss of the gel structure.[2088] X-ray diffraction studies also demonstrated changes in the nucleus pulposus and in the annulus fibrosus with advancing years. In the nucleus a tendency was noted for collagen to crystallize out of the gel structure and to become fibrous and oriented. The collagen nature of the wall of the annulus fibrosus could be identified at all stages.[889]

Papers appeared which traced the structure of the human intervertebral disc from the 3 mm. embryo through postnatal changes up to 80 years of age.[1621, 1622, 2183] Discs developed from dense mesoderm which differentiated early. Perinotochordal tissue connected the vertebrae early in fetal life, forming a continuous cartilaginous column. Later this differentiated into the fibrocartilaginous components of discs, and served also as a source for growth of the nucleus during postnatal life. During the fetal period the nucleus evolved by mucoid degeneration of some cells of the notochord. Fibers and cartilage cells appeared after birth. The annulus fibrosus differentiated early in fetal life, and from the time of earliest appearance was anchored to cartilage plates which had evolved by an extension from vertebral bodies. During fetal life the nucleus remained avascular, only the outer lamellae of dorsal portions of the annulus being supplied with very small vessels.[2183] After birth, vascularity of the annulus was obliterated, disappearing entirely by the age of 20. Thereafter the discs were dependent for nutrition upon diffusion from contiguous structures, a factor which may be in part responsible for degenerative changes.[1786] With increasing age, fibers in the annulus became coarsened and hyalinized, while in the nucleus pulposus the notochordal element was gradually replaced by fibrocartilage. Later, the fibrocartilage became progressively coarsened and desiccated.[1622]

Pathology and Pathogenesis. The pathology of disc degeneration and protrusion was reviewed in a number of papers.[378, 631, 819, 1299, 1352, 1786, 1915, 2053] Progressive degeneration of the annulus, with loss of elasticity and resilience, leads either to thinning or to incomplete posterior rupture. This rupture may occur either in the course of usual activities or as a result of trauma. The annulus is then unable to contain the nucleus pulposus in a central position. Even before protrusion, shifts of the nucleus from a central position lead to abnormal stresses on other structures. Vertebrae are no longer parallel and the nucleus, which is

the fulcrum of the intervertebral joint, lies either anterior, posterior or lateral to its usual position. Facets shift and tensions on their ligaments are changed. Resultant pain leads to muscle spasm, with splinting of the involved segment. Later, extrusion of the disc takes place through a rent in the annulus. The longitudinal ligaments which reinforce the central segment of the thin posterior annulus do not extend to the lateral margins of the annulus; hence herniation usually takes place in the posterolateral direction adjacent to posterior nerve roots. Thereafter weight borne by the annulus causes that structure to flatten. In consequence, facets become jammed together with resulting development of degenerative arthritis.[1786] Injection of strong solutions of sodium hydroxide or of hydrochloric acid into the nucleus pulposus of dogs was usually followed by degenerative changes simulating those occurring spontaneously in humans. Weakening and rupture of the annulus following these injuries usually occurred posteriorly. After collapse of an intervertebral disc occurred, sclerosing and spurring of adjacent vertebral bodies were sometimes noted.[671]

It was stated that repair of the annulus is a rare phenomenon and that normal physiologic status is never restored. The nucleus does not regain normal elasticity, and it is doubtful whether the annulus ever heals completely.[619]

Relationship to Trauma. Acute trauma may cause a disc to protrude in a younger individual. However, this was believed to be a rare occurrence. In the absence of litigation, patients seldom gave a history of severe acute injury such as occurs during lifting, twisting the body or falling. In general, degenerative changes in the disc were believed to precede trauma, which should be considered only a predisposing or precipitating factor.[631, 1233, 1560, 1786, 1848, 1936, 2289] The term "sprung back" was suggested to designate the condition resulting from forced flexion of the vertebral column, such as may occur in certain types of injury. Both anterior and posterior structures may be damaged at the same or different levels during flexion injuries. Prolapse of nuclei may result.[1548]

It was suggested that most of the reported cases of disc degeneration following lumbar puncture were actually due to infection of the disc rather than to simple trauma. It was noted that in 37 of 58 cases reported in the literature meningitis was present at the time of lumbar puncture, and that in many the course was strikingly similar to that observed in a patient in whom septic necrosis of the disc was proved to have followed injection of Diodrast into the disc.[732] [The incidence of "sciatica" was not noted for this series. Reports of disc injuries following lumbar puncture have not appeared frequently in recent years, although the frequency of this accident has probably not decreased. This is an important subject and additional information would be useful.—Ed.]

Calcification of Intervertebral Discs. The pathogenesis of calcification occurring in discs remained unknown. Trauma, inflammation, senile degeneration and "abnormal calcium metabolism" were suspected. The condition was seen frequently in far advanced cases of ankylosing spondylitis. Sandstrom noted that calcification of the disc occurred (a) peripherally either in end plates or in the annulus fibrosus, or (b) centrally in the nucleus. The more frequent peripheral calcifications were generally permanent, whereas central calcifications could be either permanent or transitory. The clinical significance of central calcification was questionable, although several patients had thoracic pain; it was at times associated with calcification of tendons elsewhere. Usually the peripheral type of calcification was asymptomatic. Transitory disc calcification has been observed among patients receiving large amounts of vitamin D, and extensive zones of calcification have occurred in patients with generalized calcinosis.[1834] Six patients with protrusion of calcified discs and accompanying compression of the cord were reported.[2062] [Calcification of the intervertebral discs is a feature of alkaptonuric arthritis, which is discussed in a separate section.—Ed.]

Cervical Discs. Protrusions in the cervical region constituted less than 10% of all disc problems. Common complaints were occipital headache and pain in the cervical region; pain also occurred in the shoulder or scapular region, often radiating into the arm, forearm or hand. Again, manifestations were divided into three groups: (a) central disc herniation and transverse cord compression; (b) paramedian herniation and resulting Brown-Séquard syndrome; (c) lateral herniation and compression of nerve roots. Patients with compression of the cord were rare in comparison with those with root compression. Patterns of sensory loss associated with cervical discs were described again in detail in numerous papers.[485, 818, 1071, 1093, 1265, 1322, 1530, 1531, 1546, 1597, 1672, 1676, 1849, 1858, 2180]

In one series of 120 patients, eight had central lesions and presented many bizarre signs and symptoms. In two instances the original diagnosis was amyotrophic lateral sclerosis.[485] Symptoms resulting from lateral protrusion of cervical discs may cause several syndromes, e.g., (1) a syndrome resulting from pressure on one root, (2) a vertical multiple root syndrome resulting from compression of one root with traction on either the root above or the one below, and (3) a horizontal multiple root syndrome resulting from compression of one root and accompanying tug on the opposite root. These syndromes may be either acute or chronic in type and due to compression of either ventral or ventrolateral aspects of the cord. In some instances, symptoms resulted from various combinations of pressures involving either single roots and the cord, multiple roots and the cord, or horizontal multiple roots and the cord.[1849]

A variety of pathologic lesions of cervical discs, with or without associated osteoarthritic changes, was described.[1672] Anomalies of bone, ligaments or muscles which allow an increased range of motion predisposed to disease of the intervertebral disc.[1636] Because range of motion is greater in the region of the lower cervical segments, protrusions of discs were most frequent between the sixth and seventh cervical segments, and next most frequent between the fifth and sixth cervical segments. Acute trauma was not frequently encountered as an immediate cause of lateral disc protrusion; more often it preceded central protrusion.[1849] But cervical disc degeneration was regarded as a common late sequel to "whip-lash" injuries of the cervical spine.[1518]

Thoracic Discs. Protrusion of discs in the thoracic region was rare, presumably comprising less than 0.5% of all disc protrusion.[818, 1313] Cyriax suggested that this condition may be more frequent than is generally believed, since these lesions do not produce so characteristic a sequence of events as do lumbar and cervical disc lesions. Neurologic signs are conspicuously absent. Symptoms resulting from this condition are readily confused with those of fibrositis, pleurodynia and intercostal neuralgia or visceral disorders.[469]

The usual location of pain attributed to thoracic disc protrusion was in the mid-dorsal region, generally on one side but occasionally about the midline. Sometimes pain appeared in the anterior or sternal regions. Characteristically it was aggravated by motions of the trunk and by deep inspiration. It was not unusual for the patient to experience both unilateral posterior thoracic pain and a referred type of pain in the anterior or anterolateral portion of the chest. A rare manifestation was unilateral substernal pain brought on by flexion of the neck. Symptoms resulting from thoracic lesions usually lasted only a few days and often followed prolonged flexion or compression of the affected segment. The first symptom resulting from compression of the cord by a protruding thoracic disc was a "pins-and-needles" sensation in the feet.

Although a small area of cutaneous hypersensitivity or hyposensitivity was occasionally demonstrable, sensory findings were of little value in making the diagnosis or in establishing the level of thoracic disc protrusion. Persons with this condition should avoid strains resulting from the carrying of heavy objects, should maintain an erect posture and avoid sitting with the back flexed.[469, 1313] Results of surgery in 11 patients were "not such as to foster complacency."[1313]

Lumbar Discs. A large number of papers dealt with lumbar disc protrusions; many were in the form of review articles.[29, 309, 378, 631, 818, 819, 871, 1352, 1517, 1786, 1915, 2289] Signs and symptoms resulting from the usual type of lumbar protrusion are now well known. Low back pain resulting either from bulging of discs or from midline protrusions associated with distention of posterior longitudinal ligaments may reflect an intrinsic sensory innervation of these structures. Evidence favoring this view was obtained at the time of laminectomy performed under local skin anesthesia. The ligamentum flavum was found to be insensitive. Pressure on the posterior aspect of a vertebral body did not produce pain unless the pressure was transmitted in such a manner as to produce movement of an involved disc. When pressure was exerted directly upon the disc, the patient experienced pain deep in the lumbosacral region. This sensation was not abolished by injecting an anesthetic agent into the nerve, indicating that the pain mechanism within the disc is independent of the nerve roots.[1915, 2242]

Diagnosis. Symptoms and physical findings characteristic of protruding discs, as well as descriptions of the special procedures employed when this condition was suspected, were reviewed in numerous publications.[112, 818, 819, 820, 1786, 1915]

Patients in whom sciatic pain was accompanied by limitation of straight leg raising to less than 40 degrees generally were found to be suffering from protrusion of a disc. Those in whom straight leg raising was limited to only 70 or 80 degrees generally did not have disc protrusion.[352] A refinement of the straight leg raising test was carried out by flexing the knee approximately 20 degrees after the point had been reached where pain was produced. Thereafter digital pressure was applied sharply to the middle of the popliteal space over the posterior tibial nerve. If the patient experienced sciatic pain, nerve root involvement was thought to be present.[449] A sign present in some cases of protruding discs in the lower lumbar region consisted of hyperalgesia and muscle spasm observed after stimulation of the skin over the back by stroking with a pin.[1415] The injection of a Novocain solution into discs was considered helpful for determining the cause of low back pain in certain instances. Temporary disappearance of pain, tenderness, muscle spasms and restriction of motion pointed to the disc as the source of pain. It was seldom necessary to resort to this procedure.[978, 1915] The character and duration of pain relief afforded by intravenous Myanesin were thought to be helpful in predicting those patients who could be expected to respond to conservative measures.[1848]

Cerebrospinal fluid protein in excess of 100 mg. % and xanthochromia were unusual findings in disc protrusion; they more often were due to spinal neoplasm.[444] Among 80 patients with protruding discs, the spinal fluid protein level exceeded 40 mg. % in 54 cases. The average value for those with an elevated level was 72 mg. %.[26] Others estimated that elevated levels of protein are found in only half the cases with protruding discs.[818]

Cysts involving either perineural or epidural structures in the lumbar and sacral regions may cause symptoms similar to those resulting from protrusion of

a disc.[1855] Other conditions which should be considered in the differential diagnosis of protruding discs include tumors of the cauda equina and the spinal cord, metastases of carcinoma, multiple myeloma, arachnoiditis, spondylolisthesis and other congenital anomalies. Osteoarthritis and rheumatoid spondylitis must also be taken into account in the differential diagnosis.[444, 535, 786, 818, 819, 1595, 1751]

Roentgen Examination. Roentgenograms were necessary to exclude the presence of malignancies, other destructive lesions, structural abnormalities and arthritis. Narrowing of an interspace indicated destruction of a disc and not necessarily protrusion. An interspace may appear to be normal even though the disc has prolapsed.[444, 818, 819, 1497, 1531, 1849] Other roentgenographic evidences of disc degeneration included altered apophyseal facets, sclerosis of the surfaces of vertebral bodies adjacent to damaged or protruding discs, decrease in size of neural foramina and formation of marginal osteophytes.[878, 1352]

Discography. This procedure, first proposed in 1948 by Lindblom, involves injection of individual discs with Diodrast, using a 26-gauge needle and fluoroscopic control.[1296] From 0.5 to 2.0 ml. of a 35% Diodrast solution are injected. With this procedure it was possible to differentiate between a normal disc, a degenerated disc and a posterior disc protrusion.[377, 380, 484, 626, 732] In one instance an anterior protrusion was detected.[376] This method of direct visualization of the pathologic process was contrasted with the indirect evidence afforded by myelography.[580]

Myelography. Some workers employed this procedure in a routine manner during investigations of patients with either backache or sciatica.[594,1283, 1672, 2289] Others believed most protruding discs can be detected with simpler tests, and that myelograms should be reserved for atypical cases,[1158] for determining the exact level of a protrusion when surgery was contemplated,[26, 819, 820, 1158, 1254, 1497, 1849] for distinguishing between tumor and disc,[1849] and for ruling out multiple lesions.[26, 501, 1672] Accuracy in diagnosis was improved for some workers by the taking of multiple "spot" films.[246] Pantopaque has been employed for myelographic studies in this country during recent years to the exclusion of almost all other products.[1672, 1849] It was advised to remove as much Pantopaque as possible after the examination. Backache and radiating pains were attributed to injury of the cauda equina during Pantopaque removal from the subarachnoid space.[1283] Fever and slight meningeal irritation were occasionally observed after the procedure.[1849, 2289]

Accuracy of diagnosis with the aid of myelograms ranged from 68%[19] to 95%.[1672] The accuracy of this procedure depended upon whether myelograms were employed in every instance or used only in the event of a difficult diagnostic problem. Some considered evidence obtained from the history and physical examination to be more important than the myelogram.[673, 1158] Berg observed alleviation of symptoms spontaneously or in response to conservative treatment, despite persistence of myelographic abnormality.[165]

Treatment of Protruded Discs. Although problems associated with protruding discs are better understood today, enthusiasm for surgery was considered still to be too high in some quarters. Patients with protruding discs should not be submitted to surgical treatment until after a thorough trial of conservative management.[1569] The only exceptions were those rare instances of "giant" herniation associated with disturbances of sphincters and other evidences of pressure on the cauda equina. Elective indications for surgical treatment included a severe, protracted attack of sciatica, repeated episodes with incapacity, failure to improve with adequate conservative therapy, and an economic situation in which the patient cannot afford to continue conservative therapy indefinitely.[1475]

Conservative treatment of protruding discs consisted of rest, support and traction.[471, 818, 819, 1915, 2289] A period of complete rest in a bed fitted either with a firm mattress or with a plywood board between the mattress and bedspring was considered as effective as leg traction.[1941] Applications of heat, massage, manipulation and analgesic drugs were recommended again. Some approved the use of Tolserol and intravenous procaine.[1848, 1869] Attempts to measure the mechanical effects resulting from leg traction at the time of exploratory operation yielded essentially negative results. When traction was applied to the legs, action currents could be demonstrated arising in the muscles of the legs, thighs and gluteal regions, but not in paraspinal or abdominal muscles.[1812] [This indicated that traction applied to the legs did not affect the paraspinal or abdominal muscles.—Ed.]

Manipulation was again advocated for treatment of protruding discs,[2053, 2260] although it was recognized that this entailed notable risk. Massive disc prolapse following manipulation was reported.[868] Myelographic studies made before and after manipulation showed no change in 11 of 12 patients; the twelfth showed slight increase in the size of the defect.[2260] The addition of "counter-torque" suspension was also recommended.[433] For ambulatory patients who experience recurrent or continuous pain, intermittent traction was advised.[470, 471, 2053] Avoidance of stooping and lifting and the support of well fitting belts or corsets were approved. Exercises were recommended for use after subsidence of the acute pain.[2289] Among the considerations which precede a decision to operate for protruded discs, careful evaluation should be made of the ability of each patient to withstand pain. If the patient was neurotic, results of surgery were generally poor.[309, 1158] [Obviously, the diagnosis of neurosis should be made before and not after surgery is performed.—Ed.]

Conservative management for painful cervical disc protrusions usually included rest in bed with traction (five to eight pounds) continuously applied with the aid of a halter. Judovich advocated intermittent motorized traction with much heavier weights.[1095] Others used intermittent traction for milder cases. Applications of heat, massage, muscle-relaxing drugs, sedatives and analgesics were also approved. Surgical intervention (decompressive laminectomy) was recommended for patients in whom conservative therapy failed and for those in whom paresthesia or muscle weakness was present. Symptoms resulting from pressure on the spinal cord may not be completely relieved by surgery.[1071, 1531, 1672, 1676, 1849, 1858, 2180]

Technics for surgical removal of protruding lumbar discs were further refined. The mortality rate was less than 1% when the operation was performed by competent surgeons. Approximately 90% of the cases were said to be cured or greatly improved by operations. However, in 10% of the cases disabling pain persisted after surgery, and as many as 40% had lesser degrees of disability.[111, 112, 256, 309, 379, 501, 681, 726, 876, 1314, 1560, 1569, 1786, 2265] When the patient was engaged in litigation with reference to a protruded disc and alleged injuries, results of all forms of treatment were generally poor.[256, 2265] Among persons with disc protrusions allegedly originating in industrial accidents, nearly a third had failed to return to work as long as two to five years after surgery.[19] Similarly, the result of treatment among private patients was better than among patients treated in Veterans Administration hospitals.[2289] But of 303 coal miners operated on only after conservative treatment had failed, results were considered satisfactory in 90%.[719]

Spinal fusion was again approved for patients showing instability of the spine in association with a protruding disc.[726, 820, 1625] Others approved spinal fusions only for those instances complicated by spondylolisthesis.[26] Cloward advocated spinal fusion by putting bone grafts in place of the extirpated disc in every instance.[377, 378, 379]

Causes for failure following operations for protruding discs were numerous.[61]

Among 67 patients in whom a second operation was done, dense adhesions were found about nerve roots in 24. Other causes for failure in this group included new herniations either opposite to the previous one or at other levels, recurrence of protrusion at operative sites and "missed" herniations.[835] When the operation was complicated by occurrence of an arachnoiditis, severe and persistent incapacity was apt to result.[1960] Foraminotomy proved effective for patients in whom a foramen was narrowed, either by settling of vertebrae following disc degeneration or by spurs at posterior margins of vertebral bodies.[835, 1672]

Sciatica

The term "sciatica" is well established, descriptive and useful, but it should not be looked upon as a diagnosis. In the past, neuritis, neuralgia, hip joint disease, sacro-iliac disease, congenital malformations, mechanical disorders and myopathies have been designated as possible causes. Most of these have been evaluated and discarded; today, prolapsed intervertebral discs are assumed to be the cause in most cases.[28, 29]

Major sensory components of the sciatic nerve arise from the first sacral and from the fourth and fifth lumbar roots, supplying pain, touch and temperature fibers to the skin. They also supply pain, position sense and deep pressure fibers to muscles, tendons and to capsular structures of foot, ankle, knee and sacro-iliac joints. Posterior joints of the spine and the annulus fibrosus of lower lumbar intervertebral discs are also supplied by recurrent nerve fibers from these segments. Few or no pain fibers to the abdominal or pelvic viscera arise from these roots.[112] Lesions responsible for sciatica may occur in the nerve roots, in the lumbosacral plexus, or in the sciatic nerve. Lesions of the nerve roots were responsible for 95% of cases of sciatica; of these lesions, 90% were protruding intervertebral discs. Other lesions such as neoplasms, cysts, vertebral fractures, epidural abscesses, osteomyelitis, syphilis and arthritis also may cause sciatica by affecting nerve roots. The radicular syndrome resulting from any of these consisted of pain in the back, with radiation or extension into the extremity. Lesions of the sciatic nerve and lumbosacral plexus were responsible for only 5% of the cases of sciatica and may be differentiated from the radicular syndrome by the severity and location of the symptoms and signs.[1475]

Diabetes, alcohol, arsenical poisoning, dietary insufficiencies and arteriosclerosis of the vessels supplying nerves may cause sciatic neuritis.[28, 112, 535, 1475] A sensory pattern characteristic of radicular sciatica consisted of an unusual disturbance of superficial and deep sensibility corresponding to neither the peripheral nor the segmental innervation. The involved region included the lateral aspect of the leg and thigh and the lateral three toes. The cause was said to be radiculitis of the first sacral root.[883a]

Previous episodes followed by remissions suggested that protruded discs were responsible, whereas a progressive course with severe night pain suggested neoplasm. A protruded disc seldom caused severe tenderness to percussion over the spine, but this was a common finding in infection or neoplasm of the spine.[535] Intraspinal tumors originating below the level of the tenth thoracic vertebra causing sciatica were easily mistaken for protruding discs. Neoplasms in this region were discovered at the time of surgery in 4% of the cases in one series of patients who underwent operation, presumably for protruded discs.[444, 535] Lumbar and sacral cysts were again reported as causing low back pain and sciatica,[1855] as was a retroperitoneal tumor[41] and tumoral calcinosis.[1751]

Gout and Gouty Arthritis

Sustained interest in gout and in the associated abnormalities of uric acid metabolism was reflected in a number of reports. The total impression gained from this literature is one of rapid progress in control of an ancient disease. Numerous articles reviewed the essentials of diagnosis and the changing concepts in treatment.[731, 858, 862, 863, 2098, 2099, 2100, 2101, 2225] Experience was gained with newer agents for the control of acute attacks. An attitude of optimism toward the management of chronic gouty arthritis was evident as a result of long-term studies with uricosuric agents. Clinical investigation employing isotope tracer technics pinpointed aberrations from normal in the formation of uric acid from precursors in some but not all patients with gout. Primary or classic (hereditary) gout was clearly distinguished from gout secondary to other disease, usually involving the hematopoietic system.[860]

Incidence and Clinical Data. Of 1,570 cases of arthritis and allied disorders in three English hospitals, there were 77 cases of gout (4.9%).[2254] Among males admitted to the medical service of a large Chicago charity hospital, the annual incidence of gout in Negro men ranged from 0.06 to 0.1%; in the same period the annual incidence of gout in white men ranged from 0.04 to 0.02%.[1527] Gout was reported in a Negro woman, claimed to be the first such case on record,[1635] and in three Filipinos.[1354] In polycythemia, gout occurred in 15% of 293 cases reported in the literature.[954] In a series of 65 cases, the average age of onset was 36.2 years; the youngest patient was a girl of 14 years, and there were seven females (9%).[1432] In another series of 115 cases, 15 were females (13%).[1374] Attention was again called to the fact that the onset can occur at a younger age than is generally appreciated.[1057] The initial attack of gout was observed as early as the first decade or as late as the eighth decade; in general, the later in life the first attack developed, the milder the disease and the less the incapacity.[2101]

Some data supported the concept advanced by Wood Jones (Tenth Rheumatism Review) that acute attacks of classic gout have as their basis a disturbance of the vasomotor nerves controlling the periarticular plexuses. Plethysmographic determinations yielded clear evidence of increased blood flow through the affected limb during an acute attack,[108, 2280] and the same phenomenon was inferred from oscillometric studies.[2280] Decrease in blood flow paralleled clinical improvement in response to treatment. [No explanation was offered for the observation that often the blood flow was also increased to as great a degree in the unaffected contralateral limb.—Ed.]

The frequency of tophi varied from 18.1% in one group[2254] to 38%;[1432] but tophi were seen in only 2% of patients at the time of the initial attack.[2037] These late manifestations may not develop in patients with a mild form of the disease.[2101] Tophaceous deposits of urate in the bulbar conjunctivae were described in two cases of advanced gout.[1486, 2305] [Garrod briefly mentioned two such cases in the Third Edition (1876) of his *Treatise on Gout and Rheumatic Gout.* We are not aware of other well documented reports of tophi in this rare location.—Ed.] Ocular manifestations in this disease may include conjunctivitis, scleritis or episcleritis, iridocyclitis, tenonitis and, rarely, keratitis; a combination of these constituted the "hot red eye" of gout. Such inflammatory reactions were recognized as occurring after cataract extractions in gouty patients.[1436]

"Secondary gout may occur, occasionally, in the course of primary polycythemia, secondary polycythemia, myeloid metaplasia, chronic leukemia, Cooley's anemia and other chronic hemolytic anemias in adults, pernicious anemia, and in

the malignant lymphomas; it is rarely if ever associated with the hyperuricemia of chronic nephritis or multiple myeloma."[860] Hickling reported nine cases in association with myeloid metaplasia, and expressed the opinion that gout occurred much more commonly in patients with myeloid metaplasia involving all marrow elements than in patients with typical myeloid leukemia or typical primary polycythemia.[954] Clinical gout and urate calculi occurred in members of a family with Cooley's anemia.[1367]

The renal manifestations of gout continued to attract attention. Of 324 patients with proved gout admitted to the Ochsner Clinic during a nine year period, 14 to 17% gave a definite history of urinary calculi; such a history was obtained in only 1.23% of all admissions.[1881] However, urate calculi can occur in patients without gout or hyperuricemia. Of 117 patients with urate calculi, only 43 had hyperuricemia; of these, 32 had gout.[63] The well recognized manifestations of nephrosclerosis in gout were discussed.[860, 1404, 1432] The kidney disease in one case led to the clinical diagnosis of systemic lupus erythematosus; at autopsy, urate deposits were found in the renal pyramids.[1404]

A renal syndrome characteristic of gout was delineated and considered to result from compression on the collecting tubules by urate deposits in the pyramids and medulla, with consequent atrophy of the nephron. This "kidney of gout" had the following features: (1) absence or near-absence of protein and formed elements in the urine; (2) renal insufficiency as shown by urea clearance, dye excretion, and concentration and dilution tests; (3) marked elevation of the blood nonprotein nitrogen and urea nitrogen; (4) normal blood pressure; (5) a chronic course compatible with longevity. Three examples of this clinical syndrome were presented. It was considered a small but clearly defined entity within the entire spectrum of renal disease in gout.[1482]

Provocative Factors. The factors long known to induce acute attacks of gout (overindulgence in food and alcohol, acute infections, surgical procedures, foreign protein therapy, roentgen irradiation, insulin and liver injections, blood transfusions, worry, exposure to cold and dampness, and drugs such as penicillin, mercurial diuretics, and ergotamine tartrate) were again listed.[2099, 2101] Apparently testosterone should be added to this list. Levin and his associates recorded acute gouty attacks shortly after discontinuation of testosterone in five of nine attempts.[1271a, 1272] The production of acute gouty attacks by abrupt withdrawal of ACTH was noted in the Tenth Rheumatism Review. Kersley, Mandel and Jeffrey failed in five attempts to induce attacks after giving ACTH for a period of 24 hours or less, even with concomitant use of a high fat diet, and concluded that this was not a reliable means of inducing acute symptoms.[1148] Others gave doses of at least 40 mg. of ACTH daily for five days, and obtained withdrawal attacks in six of nine attempts.[1271a, 1272] [There is need for further information as to the consistency with which acute attacks of gout can be provoked by abrupt withdrawal after ACTH has been given for sufficient time and in sufficient dosage to produce clear-cut metabolic effects.—Ed.]

Etiology and Pathogenesis of Hyperuricemia. *Hereditary Factor.* This was again stressed as one of the most important etiologic factors in classic gout. About two thirds of Talbott's patients had a family history of gout;[2100] in another series of 77 patients, 30 relatives were claimed to suffer from the disease.[2254] The genetic determination of hyperuricemia in the relatives of gouty

patients was well recognized.[1961, 2008, 2254] [The details of these studies are available in previous Reviews.—Ed.]

The only new data were furnished by a British study, in which isolated blood uric acid determinations were made on 29 members of three families. Of these, 21 (72%) had hyperuricemia, and 11 had clinical gout.[2254] The present knowledge of genetic factors in gout and hyperuricemia was summarized as follows: (1) Asymptomatic hyperuricemia is a frequent finding in the relatives of patients with gout. A single dominant autosomal gene is probably responsible for the transmission. It is estimated that the penetrance is about 46% in the heterozygous male, and about 12% or less in the female. (2) Gouty arthritis may develop in an individual of either sex who possesses a sufficiently elevated serum urate level for a sufficient length of time. This is less probable in the female because of the lower normal serum urate level in women and a lesser effect (i.e., lower penetrance) of the abnormal gene in this sex.[1961]

Mechanism of Hyperuricemia. Tracer studies with labeled uric acid have demonstrated an increase in size of the miscible pool of urate and decreased rate of urate turnover in patients with gout (Tenth Rheumatism Review). This concept was substantiated by extensive additional observations.[196] Further application of isotope technics established that this abnormality was associated with overproduction of uric acid, at least in the 25% or more of cases of primary gout who habitually excrete large quantities of urate on a low purine, restricted protein diet.[860, 2044] Glycine labeled with N^{15} was fed in a single dose to normal and gouty subjects and the distribution of isotope among the nitrogenous constituents of the urine determined during the succeeding nine days. Under the conditions of study, normal subjects excreted about 0.3% of urinary isotope as uric acid. In patients with gout who excreted large quantities of uric acid, this figure was three times normal, or approximately 1%; there was unequivocal evidence of an abnormally rapid incorporation of dietary glycine into the uric acid.[154, 155] In gouty patients with normal levels of urate excretion, the excretion of isotopic uric acid after glycine-N^{15} feeding fell within normal limits.[155, 1513] "This finding leaves open the possibilities either that the mechanism of the metabolic defect is not the same in all patients diagnosed as gout or that the various patients were studied at different phases of their disease" (Stetten[2044]). [During the period covered by this review, such studies were carried out on three normal subjects, two gouty patients who were "high urate excretors," and three gouty subjects with normal urinary urate excretion. More recent studies using glycine labeled with C^{14} have yielded essentially the same information. —Ed.] It was suggested that this rapid incorporation of isotope into uric acid in some gouty patients was due to direct conversion of dietary amino acids to purines without intermediary incorporation into nucleic acids.[860, 2043, 2044]

In contrast, in patients with secondary gout the accumulation of N^{15}-labeled urate in the urine after glycine-N^{15} feeding was much slower, reaching its peak on the tenth to fifteenth day. Such results were obtained in a patient with gout associated with polycythemia secondary to congenital heart disease,[2308] and a patient with myeloid metaplasia associated with gouty arthritis.[1242] While the total amount of isotope incorporated into uric acid was about twice that obtained in normal subjects, its rate of appearance was consistent with the relatively slow turnover of nucleic acids or nucleoprotein. Therefore, secondary gout "appears to be due, not to an inborn error of metabolism, but rather to an acquired acceleration in the degradation of nucleic acids" (Gutman[860]).

Studies with isotopic uric acid provided further evidence that uricolysis does occur in man. Following the injection of labeled uric acid, the amount of uric acid synthesized daily was calculated and compared with the urinary excretion of uric acid. In five of six such determinations on normal subjects, from 68 to 77% of the uric acid synthesized by the body was excreted as urinary uric acid.[313] In another study, isotopic nitrogen was demonstrated in urinary ammonia and urea following the intravenous injection of isotopic uric acid. It was estimated that about 18% of the injected uric acid was degraded to other nitrogenous products, about 78% excreted unchanged in the urine, and about 6% excreted in the feces. This proportion was not significantly altered when intestinal bacteriostasis was maintained by an oral sulfonamide, indicating that the degradation to other nitrogenous products was not due to action of bacteria on uric acid excreted into the gastrointestinal tract.[2296] [These studies have reopened the theoretic possibility that the hyperuricemia of gout may be due to decreased destruction of uric acid. The isotope method does not permit direct study of this possibility, since in the gouty patient the contribution to the miscible pool from uric acid in the "solid phase" cannot be distinguished from newly synthesized uric acid.—Ed.]

There were no new data to support the concept of a specific impairment of renal excretion of urate in gouty patients. Nevertheless, the capacity of the kidney to excrete the load of urate delivered to it was considered an important factor in the course of the disease, particularly with respect to the deposition of urate in the tissues.[860] Bene and Kersley investigated the possibility that the physical state of uric acid in the plasma might be responsible for the undue retention of uric acid in gout; they found that an average of 94% of the plasma uric acid was ultrafiltrable in both gouty and nongouty subjects.[153]

No new data appeared to elucidate the role of androgenic hormones in the pathogenesis of the hyperuricemia of gout (Tenth Rheumatism Review). In contrast to previous reports, Butt and Marson found the 17-ketosteroid excretion of 33 gouty patients to be in the normal range. The determinations were done by a polarographic method, and results compared with normal controls ranged according to age and sex.[312] [Others, using colorimetric methods, have continued to find 17-ketosteroid excretion somewhat lower than normal in gouty patients. But it has become evident that such observations do not necessarily imply diminished production of androgens. There is at least suggestive evidence that gouty patients excrete a smaller proportion of adrenocortical steroids as 17-ketosteroids than do normal people. Further studies of the metabolism of steroids in patients with gout may well clarify this problem. In the meantime, it no longer seems necessary to postulate the existence of the hypothetic "gouty androgen" referred to in the Tenth Rheumatism Review to explain these observations.—Ed.]

Pathogenesis of Acute Attacks. *Relationship to Uric Acid.* There was agreement that the concentration of uric acid in the blood is not responsible for the acute attack of gout.[402, 1386, 2099] There is no evidence to indicate any acceleration of deposition of uric acid immediately before or during acute articular symptoms.[2099] Other indications that uric acid is not the precipitating factor were: acute attacks cannot be produced by feeding or injecting uric acid; many patients with sustained high serum urate concentrations do not develop acute attacks of gouty arthritis; and many joints containing urate deposits give no acute symptoms.[858]

Relationship to Adrenal Cortical Function. Evidence for and against the theory that acute attacks of gout are related to temporary hypofunction of the pituitary-adrenal system was summarized in the Tenth Review. Studies utilizing more accurate methods for determining adrenal cortical function failed to support

this concept. The urinary excretion of 11-hydroxycorticoids (determined as neutral lipid-soluble reducing substances), the circulating eosinophil level and the sodium concentration in the sweat and urine were followed during and between 12 attacks of gout in six patients. In two subjects, metabolic balances were obtained for periods of 90 and 161 days, respectively. Observations were made during spontaneous attacks, and during attacks induced by withdrawal of ACTH and of testosterone. The results indicated no evidence of pituitary or adrenal cortical hypofunction in relation to acute attacks of gout, and no significant difference between the responses of normal and gouty patients to administration of ACTH or to its withdrawal. Neither did these studies support the concept of a "gout cycle" with respect to electrolyte metabolism.[1271a, 1272]

Laboratory Data. Interest centered almost exclusively on urate levels in body fluids. The plasma urate level was stated to be 0.2 to 0.9 mg.% higher than whole blood urate levels.[2254] The whole blood urate levels in four subjects showed variations throughout the day as great as 0.8 mg.%; this variation had no relationship to meals.[2254] Daily determination of blood or plasma urate in patients with gout showed large day-to-day fluctuations in some patients.[1386] The serum urate level did not appear to be greatly influenced by altering the purine content of the diet. The mean serum urate level of eight patients with gout on their usual diet was 7.6 mg.%; after seven to 11 days on a low purine diet, the mean level was 6.4 mg.%; it returned to 7.7 mg.% after seven to 11 days on a high-purine intake.[1374]

The plasma urate level was again reported to be higher in men than in women; this is true of normal people, of gouty people and of the hyperuricemic relatives of gouty people.[2008] The mean serum urate levels and standard deviations, as determined by differing colorimetric method in two series of normal subjects, were as follows: 91 men, 5.3 ± 1.7 mg.%; 96 women, 4.3 ± 1.0 mg.%;[860] 50 men, 4.54 ± 1.08 mg.%; 50 women, 3.82 ± 1.00 mg.%.[1374]

Since changes in uric acid levels in body fluids are a fundamental consideration in much of the current research in the field of gout, an evaluation of available methods of measuring uric acid is pertinent. A variety of methods based on colorimetry has been used.[635, 1041, 1470, 1553, 1612] Disadvantages which these methods have in common are the loss of uric acid with the precipitation of protein, and the inhibition or augmentation of color production by materials other than uric acid in the filtrates. Several modifications of colorimetric methods were reported.[59, 183, 938] The use of uricase to eliminate errors due to nonurate chromogens was of no advantage in routine laboratory determinations of plasma urate by colorimetric methods; "true uric acid" averaged only 0.2 mg.% below the apparent uncorrected values.[1086] However, use of this enzyme improved the specificity of colorimetric determination of uric acid in the urine.[1937] By taking advantage of the specific ultraviolet absorption bands of various purines, Kalckar in 1947 devised highly specific methods for determination of purines and uric acid.[1099] A simplified method for preparing the uricase needed in this method was described,[1512] and the method has been used in certain investigative studies.[1272] Praetorius obtained values for plasma urate by this technic which are somewhat higher than those obtained by colorimetric methods; in 87 normal males, the values ranged from 2.5 to 9.7 mg.%.[1681] [Until there is agreement on a standard method of determination, it seems important that workers in this field clearly indicate the method used and the range of normal values obtained in their laboratories. The range of serum or plasma urate in normal subjects in different age groups of both sexes, as well as in gouty individuals and in their relatives, requires further study.—Ed.]

Pathology. In the few reports of autopsied cases, interest centered around the renal changes.[372, 1152, 1404, 1482] Again, some believed the compression or obstruction of the collecting tubule by medullary and pyramidal urate deposits to be chiefly responsible for the renal lesion.[1482] Additional factors, including nephrosclerosis, were considered equally important by others.[1152, 1404] Amyloidosis secondary to gout was described.[372]

Deposits of urate crystals were not found in the central nervous system and its coverings, but one case was reported with severe damage from urate deposition in contiguous structures in the spinal canal.[1196] A distinction was made between urate deposits in avascular tissue (hyaline and fibrous cartilage) and in vascular tissues (synovial membrane and bone marrow). In avascular tissue there was neither inflammatory nor cellular reaction around the precipitated urates, but in vascular tissue there was an inflammatory response with the development of the characteristic "gout granuloma."[402]

Diagnosis. Discussions of diagnosis continued to emphasize three well established criteria: the clinical characteristics preceding and during the acute attacks, the elevation of plasma or serum urate, and the therapeutic response to colchicine when properly administered.[863, 1113, 2100, 2101, 2225] Atypical cases were reported,[2037] and the occasional occurrence of equivocal blood urate levels was again pointed out.[1386] While search for tophi, with subsequent chemical or microscopic demonstration of their urate content, was encouraged as an aid to diagnosis, it was again emphasized that this pathognomonic finding appears late in the disease.[2037, 2198] "One or more nodules in the helix of the ear should connote chronic gout, the diagnosis of which should have been made years previously, at the time when acute articular distress first occurred."[2101]

Treatment of Gout

Substantial advances in the management of gout have been made in recent years. Acute attacks of gout can be terminated rapidly in most patients, and the complications of the disease can be minimized or prevented. Although there is no known cure for gout, the results with the measures now available, if adapted to the stage of the disease and the needs of the individual patient, are distinctly better than those which previously could be attained.[859, 860, 863, 1961, 2102]

Treatment of Acute Attacks. *Colchicine.* Colchicine continued to be the drug of choice in handling the acute attack.[857, 1146, 1961, 2097, 2101, 2198, 2225] Its oral use was recommended by most writers, and the importance of initiating therapy early was pointed out.[1961] The dose most frequently used was 0.5 mg. every hour, or 1.0 mg. every two hours, until the attack was relieved or until diarrhea, nausea or vomiting ensued.[857, 863, 1961, 2198] It was important that such a course be given without interruption.[2101] Although the response to this drug was usually complete, one observer found that at least 25% of 87 attacks in 46 gouty subjects showed a persistence of pain and swelling, sometimes for weeks.[860] Talbott stated that less than 5% of attacks failed to respond to a single full course of colchicine.[2101]

The intravenous injection of colchicine was recommended in selected patients with acute gout; it was claimed to give prompt and striking relief of symptoms without gastrointestinal discomfort.[814, 2074] Graham and Roberts, using 3 mg.

doses in 3 ml. of saline, obtained dramatic relief of pain within four hours in 24 of 33 patients; the response was judged to be satisfactory in six and poor in three. Gastrointestinal manifestations occurred only after repeated doses. They felt that intravenous administration "deserves a much wider application where rapid response is required and where gastrointestinal intolerance prohibits oral medication."[814] Talbott suggested that in selected cases, approximately two thirds of the full course be given orally and only the remainder be given intravenously.[2101]

The mechanism of action of colchicine remained a mystery. Additional evidence clearly indicated that it does not act through the pituitary-adrenal cortex route.[1271a, 1272, 1275, 1538] It is not a uricosuric agent.[1146, 1386] In studies with isotopic uric acid, the use of colchicine in several patients led to a decrease in the turnover rate of uric acid, and in one gouty subject there was a concomitant decrease in size of the uric acid pool. It was suggested that colchicine might decrease the rate of uric acid synthesis.[196]

Phenylbutazone. References to the beneficial effects of phenylbutazone (Butazolidin) in acute attacks of gout were numerous.[613, 863, 930, 1159, 1222, 1223, 1224, 1227, 1961, 2031, 2039] Among the various rheumatic disorders treated, the results in acute episodes of gout were most spectacular. In the largest series reported, major improvement was observed in 84% of 200 patients; minor improvement occurred in 14%, and only 3% failed to respond.[1222] In another group of 16 patients who were given doses of 800 mg. daily, 13 of 20 acute attacks were completely controlled within 24 to 48 hours; in three of these patients, the attacks had proved refractory to colchicine and ACTH.[863] In many patients with acute manifestations, the response to phenylbutazone was said to be more satisfactory than to colchicine.[930, 1222, 1223] Experience in chronic gouty arthritis was limited. In one series of 36 patients, phenylbutazone in amounts of 100 to 600 mg. per day was reported to control symptoms and to decrease the frequency of acute attacks in 27.[1222]

All who reported favorable results with this drug enumerated the reactions which may accompany its use and emphasized the risk. [Toxicity of this drug is reviewed in the section on Treatment of Rheumatoid Arthritis.—Ed.] In view of the short-term therapy required, these hazards appeared to be remote; however, vigilance was considered essential.[863]

There was agreement that phenylbutazone lowers the serum urate level.[314, 613, 863, 1159, 1222, 1223, 1224, 1814] Initially, doubt was expressed that this could be accounted for by increased urinary urate excretion.[1159, 1222, 1223] Others reported a statistically significant increase in uric acid output in gouty subjects during the administration of phenylbutazone.[195, 863, 1961] Unequivocal uricosuric effects of this drug were demonstrated in studies of urate clearance, and this effect was shown to be due to a depression of tubular reabsorption of urate. Definite uricosuric action was noted only when the plasma phenylbutazone level exceeded 10 mg.%, and the increased urinary excretion accounted for the fall of plasma urate levels in most cases. Nevertheless, phenylbutazone was not recommended for urate diuresis in chronic gout, since it was distinctly less effective in this respect than probenecid and was more likely to produce serious toxic reactions.[2307]

Hormones. Experiences with the use of corticotropin in the treatment of acute gouty arthritis were favorable in most but not all instances.[863, 1113, 1554, 1961,

[2030, 2032] It was valuable in patients who failed to receive adequate symptomatic relief from a full therapeutic course of colchicine or who did not tolerate colchicine well.[699, 857, 2097] The administration of oral colchicine in doses of 1 to 2 mg. daily, in divided doses, for several days after the cessation of ACTH therapy, introduced by Wolfson in 1950, has been widely adopted.[857, 863, 1554, 1961] This combined corticotropin-colchicine regimen had the advantage of providing rapid relief and of not causing gastrointestinal upsets. Intramuscular ACTH in an aqueous menstruum was used in 40 acute attacks; with 100 mg. daily doses, inadequate responses occurred in 30% of cases, but the use of larger initial doses (up to 200 mg. per day) reduced poor results to 10%.[863]

Cortisone was considered to be of limited value in acute gout by most qualified observers.[72, 711, 863, 1554, 2097, 2099, 2100] Its action appeared to be slow and uncertain, and relatively large doses (200 to 300 mg. per day) were required to suppress the attack.[699, 857, 1554] Hydrocortisone was reported to be effective when administered into the acutely inflamed joint.[697, 985] [Some of us have been disappointed with the effectiveness of intra-articular injections of hydrocortisone into gouty joints. There is at present a surprising absence of factual information as to the effectiveness of oral hydrocortisone, prednisone and prednisolone in acute gout. —Ed.]

Reports of the action of testosterone in acute gout suggested an effect similar to but less marked than corticotropin. It was thought to be an adjunct to colchicine, and appeared to prevent relapse after ACTH treatment.[989] Definite subjective and objective improvement followed its use in five of 10 patients treated with doses of 100 to 200 mg. daily for two or three days. The response was not so rapid as with colchicine, and relapses followed its withdrawal.[1271a]

Miscellaneous Measures. Anticoagulants, heparin in one case and Paritol C (a polysulfuric acid ester of polyanhydromannuronic acid) in four cases, produced a complete remission in 24 to 96 hours. The response was described as dramatic, with approximately 80% reduction in pain, swelling and tenderness within 24 hours.[1020] [These results are of considerable interest in view of the theory that acute gout is a syndrome due to local vascular dysfunction.—Ed.] Four of five patients with acute gouty arthritis given H.P.C. (3-hydroxy-2-phenylcinchoninic acid) had prompt and pronounced symptomatic relief within 24 hours after the first dose.[1934] Clinical improvement and prolonged reduction of serum urate levels were reported in eight patients treated with a fraction isolated from postpartum plasma.[817] Results in 18 patients with chronic gouty arthritis treated with organic copper salts were reported; eight had marked improvement, five had slight improvement, and five had no improvement.[1225] [These patients continued to receive salicylates, colchicine and glycine, and continued to have chronic symptoms and acute exacerbations in one or more joints. We agree with the authors' conclusion that the results are questionable.—Ed.]

Interval Management. Objectives of management in the intercritical period were defined as prevention of acute attacks, and prevention and treatment of deformities and disabilities of chronic tophaceous gout by inducing negative urate balance.[860]

Maintenance Colchicine. The uninterrupted use of 0.5 to 2.0 mg. of colchicine daily during the intercritical periods has proved to be useful in the prevention of acute gouty attacks.[858, 863, 2099] In 31 patients treated by this program for periods varying from 18 months to four years, 18 patients showed a marked reduction in the frequency and severity of attacks, 13 returning to full employment; in eight the results were unsatisfactory, and in five instances

no definite judgment could be made.[863] "The number of patients with gout who have taken colchicine daily for a decade or more is sufficiently large to state with assurance that such a regimen is beneficial. Tolerance to the drug does not develop" (Talbott[2101]).

Dietary Restriction. Empiricism in the dietary management of gout is gradually being replaced by logical measures based on the newer knowledge of purine metabolism. There was agreement that foods high in preformed purines (meat extract, sweetbreads, liver, kidneys, anchovies, smoked meats) should be eliminated, that a high fat intake should be avoided, and that obese patients should be reduced. Some advised no additional dietary measures.[2100, 2101, 2198] Others advised still further restriction of purine intake and limited protein to 50 to 75 gm. daily, given insofar as possible in the form of plant and milk product protein.[860, 1961] On such restricted diets the daily urinary excretion of uric acid was stated to decrease as much as 200 to 300 mg.,[860] and in 71 patients the mean fall in serum urate was 1.2 mg.%.[863] The same average decrease in serum urate was obtained on low purine diets in another study with eight subjects.[1374] In a carefully controlled study, three of four healthy subjects excreted significantly more uric acid while ingesting a purine-rich diet.[2255]

Recent studies of purine metabolism gave some support to each point of view. It was recognized that purines were synthesized in the body from the simple precursors of glycine, formic acid, carbon dioxide and ammonia. [Details of these studies were summarized in the Tenth Review.—Ed.] "The usefulness of dietary regulation is of necessity limited, because of the lively biosynthesis of uric acid from the simplest precursors derived from virtually every foodstuff" (Gutman[860]). On the other hand, advocates of protein restriction pointed to studies indicating that high protein diets tended to accelerate purine biosynthesis, so that larger amounts of uric acid were formed from nitrogenous precursors. Glycine labeled with N^{15} was found to be incorporated into uric acid more rapidly when the diet was high in protein in both one normal and one gouty subject.[184]

Uricosuric Agents. There was agreement that dietary restriction was much less effective in promoting negative urate balance than were uricosuric agents. This was due primarily to the introduction of probenecid (Benemid) (p-[di-n-propylsulfamyl]-benzoic acid), a potent urate diuretic of low toxicity. It was demonstrated in a series of excellent contributions that this drug can, by long-term administration, reduce the serum urate, often to normal levels,[858, 861, 1612, 2102] minimize the deposition of urates in the tissues, and decrease the size of established tophi by the mobilization of urate crystals from the tissues.[858, 863, 2306] It was demonstrated to act by a highly selective inhibition of the reabsorption of urate in the renal tubule,[1937] producing an increase in uric acid excreted in the urine from 30 to 200% above base line levels.[1146, 1612, 1664, 1937, 2102] The increase in urinary urate excretion was often not maintained after the first few weeks of probenecid administration, but the increase in urate clearance and depression of serum urate levels persisted as long as the drug was administered. Isotope studies demonstrated a decrease in size of the miscible urate pool and an increased rate of urate turnover.[197]

The usual dosage recommended was 1.0 to 2.0 gm. per day.[859, 860, 863, 2102, 2198] Administration of acetylsalicylic acid completely nullified the uricosuric effect of

probenecid;[861, 1612, 1664] no such inhibitory effect was seen with phenylbutazone.[2307] If acute attacks occurred while the patient was taking probenecid, colchicine was used without reducing the effectiveness of probenecid. Probenecid was of no value in the therapy of the individual acute gouty attacks.[1612] Some advocated the use of probenecid in all stages of gout as soon as the diagnosis is established.[2198] The majority, however, recommended the regular administration of probenecid for those patients with chronic gout who have already developed tophi and persistent stiffness of the joints.[863]

Toxic manifestations were infrequent and usually not serious. Occasional drug rash and gastrointestinal disturbances were noted,[861, 1612, 2102] and two serious anaphylactic reactions were reported.[1189, 2100] Renal colic and urate calculi also occurred during probenecid administration;[861, 1612, 2101] this danger could be minimized by regulation of dosage and maintenance of a high urine volume.[2306] Occurrence of acute attacks during the first few weeks of probenecid administration was noted in 11 of 62 patients,[861] and in nine of 20 patients;[1612] others commented on increased frequency of attacks during this time.[2101] After four to six months of continuous therapy, there appeared to be a decrease in frequency of acute attacks.[2101]

[All of us use probenecid in patients with chronic tophaceous gout and in those patients who, because of their clinical course or sustained degree of hyperuricemia, appear to be candidates for development of these complications. Some of us would add this drug to the program of patients with frequent acute attacks of gout, in the hope that after many months of its administration the frequency of such attacks would be lessened. A few of us feel that this effective uricosuric agent should be used in all patients with gout, regardless of the severity or duration of the disease.

[It seems unnecessary to point out that probenecid does not replace colchicine in the management of gouty patients, but it is not uncommon to see patients who have been treated on this assumption. This new uricosuric agent has no value in treatment of acute attacks of gout.—Ed.]

The uricosuric action of large doses of salicylate was again demonstrated.[1146] Yu and Gutman had found that dosage of less than 5 gm. of salicylates daily had little uricosuric effect, and that few patients could tolerate such doses for very long.[2306] However, Marson initiated sodium salicylate therapy with doses of 6 gm. per day, and succeeded in maintaining 28 of 29 patients with chronic gout on doses of 4 to 9 gm. for as long as 30 months. After the first month, only three patients had significant difficulty with salicylism. Depression of serum urate level was maintained by continuous salicylate administration, and tophi disappeared in two cases. In three patients, radiologic evidence of recalcification of osseous tophi was obtained.[1373, 1374]

Other Studies on Colchicine. It was demonstrated that even USP colchicine is contaminated by other alkaloids.[1014] Systematic reinvestigation of the pharmacologic and chemical effects of purified colchicine indicated its most prominent action to be on the central nervous system; vasoconstriction and gastrointestinal effects appeared to be on a neurogenic basis.[645] Colchicine biosynthetically labeled with C^{14} was injected into mice and the distribution of radioactivity in various organs determined four hours later; a surprisingly high degree of localization was found in the spleen.[86] Therapeutic doses of colchicine resulted in moderate to marked sodium and chloride retention in both gouty and control subjects; the retention of chloride was roughly proportional to the decrease in urine volume.[1272] In contrast, colchicine produced a diuresis in rats, apparently by inhibiting tubular resorption of water.[518] Oral colchicine resembled heparin in its ability to diminish the lipemic response to alimentary fat as measured by changes in optical density of the serum.[1529]

Cinchophen Toxicity. There was only occasional reference to the use of cinchophen in the management of gout. Because of possible toxic effect on the liver, its use was reserved for those cases which are not satisfactorily controlled by other drugs and accepted methods.[2162, 2198] [No new cases of cinchophen toxicity were reported during the period covered by this review.—Ed.]

Other Studies on Purine Metabolism and Uric Acid. Excellent reviews on purine metabolism[359] and on uric acid as related to biologic processes[198] appeared. In chicks, it was demonstrated that liver xanthine oxidase is inhibited by folic acid, and that a deficiency of this vitamin is associated with high xanthine oxidase activity and hyperuricemia.[1353] Hyperuricemia in a case of nontropical sprue was corrected when the condition was treated with folic acid.[2325] [Subsequently the same worker has demonstrated no effect of folic acid on the urate metabolism of a patient with gout.—Ed.]

The assumptions used in calculation of urate pool size and turnover rate in studies with isotopically labeled uric acid were examined. In data from 26 such determinations, it was found that these assumptions were not always valid; the chief difficulty was related to variations in rate of equilibration of the injected uric acid with the miscible pool.[196] Exercise, even of short duration, resulted in depression of urate clearance for at least one hour. During exercise this depression was proportional to the decrease in glomerular filtration rate, but during the recovery period urate clearance returned to normal much more slowly than the filtration rate. The altered tubular resorption correlated with the rise in blood lactate, and could be reproduced by administration of buffered sodium lactate.[1553] The practical importance of these transient alterations was left in doubt by the finding that the 24-hour urinary urate excretion of normal subjects on a standard diet was not significantly affected by one hour of vigorous exercises.[2255]

Most workers continued to support the concept that renal excretion took place by glomerular filtration of freely diffusible urate from the plasma, with resorption of most of the urate during the passage of glomerular filtrate through the tubules.[359, 860, 2101] Studies of the effects of uricosuric agents in Dalmatian and non-Dalmatian dogs (which differ only in their renal handling of urates) indicated that these drugs act by blocking tubular resorption of urates.[1470]

The increase in urinary urate excretion following cortisone or corticotropin administration has been well documented (Tenth Rheumatism Review). Hydrocortisone was shown to have a similar effect.[416] There was still difference of opinion as to whether this augmentation of urinary excretion was due to increased formation of uric acid or decreased resorption in the renal tubule. Comparison of changes in plasma urate levels with the rate of urate excretion in dogs receiving ACTH suggested increased urate production.[635] In rats receiving ACTH there was no effect on purine synthesis, and the effect appeared to be explained entirely by a direct effect on the renal tubule.[715] In the human, both ACTH and cortisone appear to augment urate excretion by altering renal tubular transport.[1041] In studies with labeled uric acid in humans, both ACTH (four subjects) and cortisone (two subjects) increased the turnover rate, but the pool size tended to increase following ACTH and to decrease following cortisone. A uricosuric action could be postulated for both drugs, but ACTH must also have increased the rate of synthesis of uric acid.[196]

(Part II of this Review will appear in the December issue of this Journal)

CASE REPORTS

PARKINSONISM: TREATMENT WITH CURARE *

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So many drugs have been introduced for the relief of parkinsonism that one hesitates to suggest another. Their very number, however, implies that we have yet to find a satisfactory method of alleviating the distressing features of this syndrome. Curare, in repository form, has been of value in reducing and occasionally in eliminating the spasticity so commonly found in these patients, even in those whose distress remained despite full dosage of the other commonly used drugs.

Several excellent reviews of the drug therapy [1, 2, 3, 4] of this condition have appeared recently; therefore, no attempt is made here to repeat the history and background of the experiences of other investigators. The table indicates the various materials used by this series of patients prior to the curare study. None of these individuals had a surgical attack on their problem, as this work is apparently still investigative.[5, 6, 7, 8, 9] Similarly, electroconvulsive therapy [10] has not been utilized in this group.

Curare would not have been tried on these people had the solanaceous drugs, the histamines [11, 12] or the synthetics relieved their complaints. These, then, represent rather severe instances of the disease, as most individuals respond to one or another of these remedies. Usually, as the patient gains tolerance to one medicament, another will give some comfort. The table indicates that the subjects of this study, despite having run the gamut of many therapeutic modalities, were becoming increasingly incapacitated. Treatment with curare certainly has no place in the management of the patient who is doing well on some other plan. Since no specific cure exists, *and curare is not one,* the purpose of therapy must continue to be to "render the patient as happy, active and useful as possible." [13]

It is important to emphasize that the effects of curare are not on the basal ganglia [14] but rather at the neuromuscular junction, where it inhibits the transfer of the impulses from the extrapyramidal pathways of the central nervous system.

Before proceeding further, it seems in order to emphasize that curare can produce respiratory paralysis and death. In this series of cases no untoward effects were observed other than in a patient, described below, who had difficulty in walking three hours after a 50 mg. dose of repository curare. Wherever possible, the patient should be hospitalized until the proper dose is ascertained so that the antidote, edrophonium chloride (Tensilon), oxygen and facilities for the administration of artificial respiration are readily available should their use be necessary.

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Method

In 1950 curare was first used in aqueous solution to relieve the severe spasticity of a patient with postencephalitic parkinsonism who had become completely incapacitated after he became resistant to all known forms of therapy. He could not carry out any purposeful acts, had to be fed, and was bedridden. This situation had engendered a mental depression which added to his unfortunate state. A 50 unit dose of curare given intravenously over a 15 minute period relieved his spasticity at once. He could drink milk himself and could write again. However, the treatment was short-lived, and in 45 minutes the salutary effects had disappeared. It was impractical to keep this young man hospitalized, and such large doses required the presence of a respirator and an anesthetist in his room should respiratory paralysis ensue. Consequently, the material was not tried again until repository curare (Tubadil) became available. This substance can be used in the office or at home. By gradually increasing the dose to tolerance, and repeating it at intervals determined by the patient (when rigidity reappears), we have avoided any serious unpleasant sequelae. The only difficulty was observed in a female patient (case 1, described below), who went for an automobile ride after receiving the injection. She arrived home about three hours later and fell to the sidewalk, as "I couldn't make my legs work." She sustained no serious injury and was comfortable in a few hours. She had received 2 c.c. (50 mg.) of the drug. She didn't even notify me of the episode until her next visit. Each patient is given the antidote, edrophonium chloride (Tensilon), a syringe, a needle and a card (similar to that carried by diabetics), instructing anyone to administer the material hypodermically if necessary. No patient has ever had to use the antidote.

The accompanying table shows how 13 serious instances of parkinsonism fared with this form of therapy.

Case Report

Case 1 was a 60 year old white female, one of four siblings. Three have had Parkinson's syndrome, with one death. The disease is apparently not postencephalitic, though the family history might suggest it. There was no episode of illness that affected these children simultaneously at any period. The mother, a highly intelligent lady of 84, is positive about this. There was no parkinsonism in either parent or in the grandparents. The patient received various solanaceous drugs over a five year period, until she became rigid and was unable to function any longer. She was greatly disturbed emotionally because an older sister (vide supra) had just died of parkinsonism. Since the entire armamentarium of drugs had been used on her without success, she seemed a good candidate for the repetition of the curare experiment described above, and was given 0.5 c.c. (12.5 mg.) of aqueous material hypodermically. There was an immediate response, best described in the patient's own words: "It was as if I had been taken out of a straight-jacket." The effect, however, was short-lived. One hour later, after her rigidity had reappeared, she was given 0.5 c.c. (12.5 mg.) of Tubadil (repository curare). She had some lessening of the tremor and cogwheel motion of her arms in 30 minutes, but the result was not so satisfactory as under the aqueous drug (for which she repeatedly asked). Gradually the dose of Tubadil was increased to 2 c.c. (50 mg.) every third day, and on this amount she was able to come to the office alone and to travel by herself, even out of the state. She has received Artane (trihexyphenidyl) three times daily, 5 mg.

TABLE 1

Name and Number	1. M. C.	2. E. T.	3. R. S.	4. E. M. H.	5. J. J. S.	6. S. H.	7. R. D.
Sex	F	M	M	M	M	F	M
Age	60	72	44	54	50	77	73
Type of Parkinsonism*	P.S.	P.A.	P.E.P.	P.S.	P.E.P.	P.A.	P.A.
Duration	4 yrs.	6 yrs.	12 yrs.	5 yrs.	11 yrs.	8 yrs.	7 yrs.
Previous medications	Bellabulgal Artane Atropine Hyoscine Benadryl	Artane Cogentin Atropine Benadryl Pagitane	Hyoscine Gilsemium Bellabulgal Benadryl Octane Cogentin	Vinobel Atropine Benadryl Artane Cogentin	Atropine Hyoscine Benadryl Artane Pipanol	Atropine Bellabulgal Hyoscine Artane Panparnit	Hyoscine Bellabulgal Vinobel Artane Benadryl Parsidol Cogentin
Present medications with curare	Artane Cogentin	Artane Cogentin	Artane Cogentin	Artane Cogentin	Artane Cogentin	Artane Cogentin	Artane Cogentin
Dose	44 mg.	37½ mg.	37½ mg.	37½ mg.	44 mg.	25 mg.	31 mg.
Interval	Q. 7 days	Q. 14 days	Q. 3 days	Q. 7 days	Q. 6 days	Q. 14 days	Q. 14 days
Result A† B‡	S S	S U	S S	S S	S S	S U	S U

Name and Number	8. E. N. S.	9. W. A. N.	10. G. W.	11. N. D.	12. H. H. E.	13. S. N. E.
Sex	M	M	F	F	F	M
Age	61	73	60	47	81	77
Type of Parkinsonism*	P.S.[x]	P.A.	P.S.	P.E.P.	P.A.	P.A.
Duration	5 yrs.	7 yrs.	4 yrs.	15 yrs.	5 yrs.	9 yrs.
Previous medications	Hyoscine Atropine Vinobel Benadryl Panparnit Artane	Atropine Gilsemium Vinobel Benadryl Artane Mephenesin	Atropine Bellabulgal Benadryl Artane Cogentin	Rabellon Serum[xxx] Atropine Benadryl Hyoscine Artane	Artane Cogentin Panparnit Thephorin	Artane Vinobel Rabellon
Present medications with curare	Artane Cogentin	Artane Cogentin	Artane Cogentin	Artane Cogentin	Artane Cogentin	Artane Cogentin
Dose	37½ mg.	25 mg.	27½ mg.	44 mg.	25 mg.	25 mg.
Interval	Q. 5 days	Q. 10 days	Q. 7 days	Q. 10 days	Q. 14 days	Q. 14 days
Result A† B‡	U S[xx]	S S	S S	S S	S S	S S

* P.S., Parkinson's syndrome; P.A., Paralysis agitans; P.E.P., Postencephalitis parkinsonism.
† S—Satisfactory, U—Unsatisfactory (subjective by patient).
‡ S—Satisfactory, U—Unsatisfactory (objective by physician).
[x] Severe mental depression.
[xx] Relief of spasticity and cogwheel motion, but patient said he was no better.
[xxx] Mathison commission (experimental).
All patients received some physiotherapy, usually administered at home by relatives.

per dose, and Cogentin (M.K. 02 benzotropine sulphonate), 2 mg., each night recently, and the interval between her injections has been lengthened to seven days. She had one accident with this material, when she fell three hours after a 2 c.c. dose, as previously described. She considered this of small moment and did not become alarmed or take the antidote. Since then her dose has been reduced to 1.75 c.c. (44 mg.), and there has been no recurrence of her paralyzing episode. She felt better on the 2 c.c., and had become employable as a clerical worker while taking it. This was extremely gratifying to her, as she had been confined to her bed, chair and home prior to the institution of this mode of therapy.

Her improvement may have been due to the Artane and Cogentin alone. To rule out this possibility, a placebo was substituted for the curare while the other

two drugs were continued. She detected the difference at once. The change was observed objectively in a reappearance of the cogwheel motion, the rigidity and the tremor. Some synergism seems to exist between the three materials, as the discontinuance of one or the other of the oral medications necessitated closer or larger doses of Tubadil.

This experiment was tried with four other patients (cases 3, 9, 4 and 5). In each instance the patient and the observer noted a difference in the response at once. Now all patients are kept on the three drugs simultaneously.

Discussion

Curare acts on the motor end-plates and produces its paralyzing effect at that point and not at the site of the lesion in the brain, the globus pallidum. Nonetheless, the noxious impulses from these nuclei are interrupted by the curare so that the spasticity and tremor disappear. This is quite apparent to the observer, as the arms and legs can be bent easily and the cogwheel effect is dissipated. There is relief from festination in those patients who have experienced it.

Patients with severe mental symptoms might not do so well. One such failure was case 8, who was relaxed with the medication but could not carry on any useful activities. Chlorpromazine and Reserpine did not help. Even though there was objective improvement, this case must be classified as unsatisfactory, as the patient could not function any better after the treatment.

The length of salutary effect of the repository curare in the older patients with paralysis agitans was striking. Each of them could get along with injections at intervals of from 10 days to two weeks. These patients were enthusiastic about their improvement. Actually, on objective examination the change was not so marked as that observed in the younger patients. (See cases 6 and 7.) One hesitates to use still larger doses of curare under out-patient conditions. These patients were not in hospitals where effective artificial respiration could be initiated if it should become necessary. Possibly increasing amounts could be used on institutionalized individuals, where proper safeguards are at hand.

Conclusion

The incapacitating spasticity, rigidity and tremor of Parkinson's disease can be relieved with intramuscular repository curare even in patients whose symptoms were unrelieved by other, more commonly used drugs. By continuing the repository curare with, in this series, Artane and Cogentin, the doses of curare could be spaced further apart and reduced to a level where dangerous complications could be avoided.

Summario in Interlingua

Dece-tres patientes, qui habeva devenite rigide e ergo incapacitate ab morbo de Parkinson, habeva cessate obtener alleviamento ab ulle del usual formas de therapia. Alora illes recipeva administrationes intramuscular de curare repositori sub conditiones cautemente regulate pro evitar paralyse respiratori. Iste modalitate alleviava le spasticitate del patientes de maniera que illes poteva redevenir plus utile membros del societate.

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LONG-TERM SURVIVAL IN MULTIPLE MYELOMA: REPORT OF THREE CASES*

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MULTIPLE myeloma, except for the so-called "solitary" type, is considered to be an inevitably fatal disease of relatively short duration and, in the main, little influenced by therapy. In reviewing all cases of myeloma reported in the literature from 1848 to 1928, Geschicter and Copeland [1] noted that, in 425 cases, the longest survival was five years, with the average under two years. In several subsequent reports on large series of cases [2, 3, 4, 5, 6, 7] the average duration of life after the onset of symptoms was from one and one-half to two years. Experience with a series of 57 cases has confirmed this general impression. However, the survival of three of our patients for over nine years has proved of considerable interest, and details of these cases, with a discussion of certain features, are reported in this paper.

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Case Reports

Case 1. A 51 year old sheet metal worker first experienced severe back pain on lifting a heavy object in 1944. The pain persisted and was diagnosed and treated conservatively as a herniated intervertebral disc at many different hospitals. He was admitted to the Boston City Hospital in December, 1948, and while in the hospital suddenly developed paraplegia. Laminectomy revealed a tumor compressing the spinal cord which, on biopsy, proved to be a plasmacytoma. Marrow aspiration from the sternum was consistent with multiple myeloma.

Physical examination revealed only a flaccid paralysis with areflexia in the lower extremities.

Laboratory studies at that time were: hemoglobin, 15 gm.; red blood cells, 4.83 million; white blood cells, 9,500, with a normal differential; erythrocyte sedimentation rate, 6 mm.; total protein, 6.75. No A/G ratio was reported. The urine was negative for albumin and Bence Jones protein.

Roentgenographic skeletal survey revealed compression of D 10 with a loss of bony substance. No other abnormalities were noted by x-ray.

The patient was started on urethane on January 17, 1949, and despite some nausea and vomiting averaged a dose of about 3 gm. a day.

In the ensuing few months he made an excellent recovery and after discharge from the hospital continued to show progressive improvement. In March, 1950, he was fully ambulatory, and urethane therapy was stopped at this time. He continued to do well and, when seen in February, 1951, showed only minor neurologic changes in the lower extremities. Metastatic series showed no change from the films taken in 1948.

The patient was not seen again until November, 1954, when he was re-admitted to the Boston City Hospital because of severe pain beneath the left scapula. He had struck his chest with a board about two weeks before admission, and since then had experienced pain in the area, particularly on deep inspiration and on coughing. Otherwise the patient had been well and working full time.

A chest x-ray showed an osteolytic lesion in the eleventh rib posteriorly, with a fracture through this area. Definite crepitation could be felt on palpation. Since a sternal aspiration at that time revealed a normal marrow, aspiration from the rib in the area of the osteolytic lesion was attempted. The material obtained showed some increase of plasma cells but no sheets or masses of myeloma cells. Urine was negative for albumin and Bence Jones protein; total protein was 6.29, with an A/G ratio of 4.3/1.9. Paper electrophoretic pattern failed to reveal any abnormal protein.

The patient was given intense x-ray therapy to the rib lesion, and in two months showed evidence of repair of the fracture and some cortical continuity along the edges of the lesion. Although symptom-free, in December 1955 x-ray films revealed a new fracture and osteolytic lesion in the left seventh rib. Laboratory studies showed only a slight elevation of total protein with reversal of the A/G ratio. All other studies, including serum electrophoresis, were within normal limits.

Case 2. A 55 year old steamfitter's helper first entered the Boston City Hospital in September, 1947, with a history which had begun three years before of neck pain and paresthesia in his arms. These symptoms gradually disappeared, only to recur six months prior to entry, accompanied by paresthesias in his legs and a 25 pound weight loss.

Physical examination revealed a 160 pound, muscular, middle aged man in no distress. Flexion and extension of his neck produced pain locally and paresthesia in his arms. There were tenderness over the lower cervical vertebrae and hypesthesia of both upper and lower extremities, but no motor changes. The presumptive diagnosis was epidural granuloma of the cervical meninges, and because of symptomatic improvement he was discharged to his family physician for antibiotic therapy.

This afforded equivocal relief, and he returned in four months with the same symptoms plus a constrictive abdominal sensation. The only new findings were abdominal tenderness and moderately firm, sharp-edged, two fingerbreadth hepatomegaly.

Laboratory findings at that time were: hemoglobin, 11.4 gm.; red blood cells, 3.86 million; hematocrit, 36.7; white blood cells, 6,400, with a normal differential; erythrocyte sedimentation rate, 53 mm.; total protein, 7.3; A/G ratio, 3.25/4.08; nonprotein nitrogen, 30. Urine showed 3 plus albumin and Bence Jones protein. Bone marrow aspiration revealed 19% myeloma cells, which were of a relatively mature type, found in clusters and sheets. A skeletal survey by x-ray at that time failed to reveal any bony abnormalities.

With the diagnosis of multiple myeloma established, urethane therapy was instituted. Within three weeks cervical tenderness disappeared and neck motion became unrestricted. However, weight loss continued, he became anorexic, and frequent use of narcotics for the constricting abdominal sensation was required. These symptoms gradually subsided and he was discharged on a maintenance dose of urethane.

He was re-admitted in May, 1948, because of vomiting, pain on breathing and low back pain. Urethane therapy was continued, and with bed-rest his pain and vomiting diminished. Urethane was then omitted, and a total dosage of 1,300 mg. of stilbamidine was given, with no relief of symptoms and with recurrence of vomiting. Therefore, urethane was again started. During this period he was given one transfusion of 500 c.c. of whole blood. He was discharged weighing 130 pounds and with moderate relief of symptoms.

In September, 1948, he reëntered the hospital with complaints of chilliness, anorexia, eructation and constipation of five days' duration. He was slightly icteric, and his liver was one fingerbreadth palpable. Urethane was stopped. The jaundice became intense, and liver function studies indicated hepatocellular jaundice with a high degree of intrahepatic obstruction. Because of the transfusion three months previously, homologous serum hepatitis was considered to be the most likely diagnosis. Over a three month period he gradually improved, and urethane therapy was reinstituted and continued until 1952.

During the above hospitalization the patient developed severe trigeminal nerve hyperesthesia and paresthesia, and shortly after discharge this was followed by polyneuritis and, eventually, bilateral foot drop. Repeated biopsies revealed only atrophic changes in the nerves; there was no evidence of amyloidosis.

Since that time the patient has been able to get around with the aid of leg braces, but he has had numerous hospital admissions, mainly because of the polyneuritis. Although in 1951 a compression fracture was noted in the fourth lumbar vertebra, several bone marrow aspirations from different sites have shown only a few to no plasma cells. (Since 1949 he has shown no evidence of anemia or weight loss. The urine has shown a transient albuminuria, and on occasion Bence Jones protein has been present.) In December 1955 his only complaints were relative to the pain and paresthesias from the neuritis. Physical examination showed three fingerbreadth hepatomegaly, and sensory and motor changes in the face and lower extremities. Significant laboratory findings included Bence Jones proteinuria, and total protein of 9.5, with an A/G ratio of 4.4/5.1. Serum electrophoretic pattern for the first time showed a definite abnormal peak in the gamma globulin area. This determination had been run several times previously, although only during the year 1955. Bone marrow aspiration from the sternum revealed a cellular marrow with only 6% adult plasma cells. A metastatic x-ray series showed no change since 1951.

Case 3. A 62 year old laborer was first seen at the Cambridge City Hospital

on March 25, 1947, with complaints of pain in all his extremities and joints, two weeks of sharp pain in his right shoulder radiating to his fingers and producing numbness in both hands, and one day of pain in his back, neck and right lateral chest. All these pains were aggravated by motion, though not relieved by rest or position.

Physical examination revealed an asthenic middle aged man in obvious severe pain. Though there was no limitation of motion in any joint, pain was experienced on motion, and generalized muscle tenderness was noted. No deformities or palpable bony abnormalities were found. Except for markedly hyperactive deep tendon reflexes, no neurologic signs were present. The liver edge was barely palpable. There was no edema.

Laboratory data at that time were: hemoglobin, 10 gm.; red blood cells, 3.40 million; white blood cells, 14,500, with a normal differential; erythrocyte sedimentation rate, 34 mm.; nonprotein nitrogen, 70; total protein, 5.3; A/G ratio, 1.90/3.40. Urine showed a 4 plus albuminuria but was negative for Bence Jones protein. Bone marrow aspiration revealed 15% myeloma cells, which were of the mature type and were found in groups and sheets. X-ray studies of the osseous system showed multiple punched-out areas in the skull measuring from 0.5 to 1 cm. No other bony lesions were noted.

During the week following hospital admission, pitting edema occurred in the legs, and general anasarca developed. The pains continued, requiring frequent administration of narcotics. On a high protein, low salt diet, the edema gradually subsided over the next four weeks.

On the above evidence the diagnosis of multiple myeloma was established, and treatment with nitrogen mustard was attempted. However, because of violent nausea and vomiting the patient refused further treatment after the first injection of 5 mg. On May 12, 1947, he was started on urethane, 3 gm. daily by mouth, which he tolerated very well. He became much improved, developed an excellent appetite, and the edema, pain and other symptoms completely disappeared. The patient was lost to the follow-up clinic for several months, during which time he continued on urethane and increased his dose, of his own accord, to as much as 12 gm. a day. Follow-up six, seven, 10 and 12 months later revealed a 14 pound weight gain and complete absence of pain, but a mild stiffness and tingling in the hands and feet. In June, 1948, five fingerbreadth hepatomegaly was first noted. This persisted for some time but had disappeared by February, 1950. (Urethane therapy was stopped in September, 1949.) The patient continued to do well, complaining only of paresthesias in his hands and feet. A neurologic consultant noted a stocking-glove sensory neuritis in 1954 which he felt was consistent with the nonspecific polyneuritis sometimes seen with multiple myeloma.

In November 1955 the patient's only complaints related to neuritis. No physical abnormalities were noted. All laboratory studies, including electrophoresis of serum, were within normal limits. A recent skeletal x-ray survey revealed no change in the lesions in the skull.

Discussion

While multiple myeloma is a disease of relatively short duration, instances of unusually long survival have been described. Snapper [7] reported one case of a nine year survival in a series of 97 cases. Batts,[3] Gross and Vaughan,[8] Garland and Kennedy [9] and Kestersan and McSwain [10] reported cases surviving from nine to 14 years. The long survival of these patients was attributed, at least in part, to x-ray therapy administered to multiple osteolytic lesions. Davison and Balser,[11] Kirsch [12] and Coley [13] reported single cases surviving 16,

TABLE 1

Representative Laboratory Data during Course of Disease

Case 1

Date	Hgb. Gm.%	Hct. %	WBC	ESR mm.	T.P. Gm.%	Alb. Gm.%	Glob. Gm.%	NPN Mg.%	Urine	
									Alb.	B.J.
10–10–48	15	48	9,500	6						
12–13–48	15				6.47			34	0	0
3–28–49	17.5	54	2,600	4	8.30	4.80	3.50		0	0
7–23–49	18.1	50	3,600						0	0
10–19–54	14.8	51	5,500		6.2	4.3	1.9		0	0
3–25–55	14	47	4,800		5.0	3.4	1.6		0	0
8–22–55	15.4	48	5,400	0	8	3.6	4.4	24	0	0

12 and 11 years, respectively. Lichtenstein and Jaffe,[6] in a review of 35 cases, reported survivals in two cases of nine and 10 years. In 1948 Bayrd and Hall [14] described a case of classic plasma cell leukemia treated with radioactive phosphorus in 1946 at the Mayo Clinic. In a letter to *Blood*, Bayrd [15] stated that, at a recent examination, this patient was quite well and showed no signs or laboratory findings indicative of myeloma.

In our series of 57 cases, nine, including the three reported here, are living at the time of this report. The average survival time of the 48 dead patients was 15.5 months. It is of interest to compare some of the features in the three long survivals with those commonly found in the 48 patients dying of the disease. In these three reported cases it may be pointed out that: (1) a relatively small percentage of myeloma cells was found on bone marrow aspiration; (2) the myeloma cells were of the mature type; (3) Bence Jones protein and abnormal serum proteins by electrophoresis were found in only one case; (4) renal involvement was minimal; (5) bony lesions in all three cases were not extensive; (6) profound anemia was not present.

There is no question that these cases are disseminated or truly multiple myeloma. Nevertheless, in view of the scanty yield of myeloma cells from various marrow sites, and the lack of widespread bone involvement by x-ray,

TABLE 2

Representative Laboratory Data during Course of Disease

Case 2

Date	Hgb. Gm.%	Hct. %	WBC	ESR mm.	T.P. Gm.%	Alb. Gm.%	Glob. Gm.%	NPN Mg.%	Urine	
									Alb.	B.J.
3–9–48	11.4	36.7	6,400	53	7.33	3.25	4.08	30	3 plus	Positive
6–2–48	8.2		3,100	60				29	1 plus	0
12–20–48		25	5,850						2 plus	0
3–25–49	13	42	7,500	10	6.90	4.50	2.40	35	0	0
9–16–50	13		6,400	51	8.8	4.4	3.8		0	0
1–2–51		43	9,000	50	6.7				1 plus	Positive
9–8–53	14	48		40	7.9	2.2	5.7		0	0
5–29–54	13.5	40	3,500		6.3	3.5	2.8		1 plus	0
8–23–55	12.7	42	7,400	14	9.5	4.4	5.1	18	2 plus	Positive

TABLE 3

Representative Laboratory Data during Course of Disease

Case 3

Date	Hgb. Gm.%	Hct. %	WBC	ESR mm.	T.P. Gm.%	Alb. Gm.%	Glob. Gm.%	NPN Mg.%	Urine	
									Alb.	B.J.
3–26–47	10	3.40 (r.b.c.)	14,500	34				70	4 plus	
4–11–47			12,300		5.30	1.90	3.40	45	4 plus	0
5–26–47	11.8		9,600	42	6.40	2.50	3.90	18	2 plus	0
12–20–47	15.5	47	7,200		7.20	3.60	3.60		3 plus	0
7–10–48	13.5	46	8,200	42	8.30	3.80	4.50		2 plus	0
3–25–49	17	49	8,100		6.90	3.60	3.30		0	0
12–10–51	14	48	7,650	9	6.90	3.60	3.30		0	0
10–4–54	13.6	45	10,900	38	7.10	3.1	4.0		0	0
8–18–55	14.6	51	8,500	21	7.3	3.7	3.6		0	0

there seems to be good evidence that the tumor process was not extensive. Additional support for this concept may be inferred from the lack of the marked serum protein abnormality, profound anemia and severe renal damage usually seen in the case of multiple myeloma.

In multiple myeloma, as in other malignant diseases, evaluation of chemotherapy is a difficult task. While the effects of drug therapy may be assessed by amelioration of symptoms and improvement in such objective findings as anemia, rapid erythrocyte sedimentation rate, abnormal serum protein, Bence Jones proteinuria and osteolytic lesions, nevertheless, prolongation of survival in an inevitably fatal disease is the most important criterion. In the three cases presented it is tempting to attribute the prolonged survival to the intensive therapy with urethane. An article from this clinic published five years ago [16] expressed an optimistic attitude concerning the use of urethane therapy in multiple myeloma. However, a longer and more extensive experience with this drug has somewhat tempered this initial appraisal. While urethane has caused improvement in subjective and objective findings in a small percentage of cases, a reëvaluation of the survival statistics does not indicate any contribution to increased longevity by the use of this drug. Moreover, in our cases the disease apparently had existed for many months before therapy was instituted. It is therefore difficult to judge what role, if any, urethane played in the long survival in these particular cases, since in any event the course may be a very prolonged or chronic one. In this era of chemotherapy, undoubtedly other agents will be employed in the treatment of multiple myeloma. It is important to emphasize that some cases of this disease may run an unusually prolonged and relatively benign course, and that the natural history of a malignant disease may be subject to wide variation.

SUMMARY AND CONCLUSIONS

Three cases of multiple myeloma surviving nine, 11 and 11 years (and still living) are reported in this article. Certain features in common were relatively small myeloma cell population in the bone marrow, myeloma cells of the mature type, and minimal renal, protein, blood and bone abnormalities. While all three

cases were treated for prolonged periods with urethane, the benign and chronic course of the disease should probably be attributed to the "natural history" of the disease rather than to the use of urethane therapy.

Summario in Interlingua

In myeloma multiple, como in altere morbos maligne, le evalutation del effectos de chimotherapia es un difficile interprisa proque le historia natural e le curso del processo maligne pote sequer extense variationes. Durante que il es possibile estimar le effectos benefic de un therapia a drogas super le base de criterios clinic e laboratorial, le prolongation del vita patiente ultra le expectate periodo de superviventia constitue le plus convincente demonstration del valor del drogas usate in le casos de morbos letal. Myeloma multiple—un morbo inevitabilemente letal—es normalmente non-influentiabile per ulle therapia. Ben que un numero de superviventias prolongate ha essite reportate, le superviventia medie post le declaration del symptomas de myeloma es minus que duo annos, mesmo in le plus recente era del chimotherapia.

Le presente articulo reporta tres casos de myeloma multiple con superviventias de 9, 11, e 11 annos post le declaration del symptomas (e al tempore presente le patientes vive ancora). Iste casos esseva characterisate per (1) relativemente basse procentages de matur cellulas myelomatic in le medulla ossee; (2) proteina Bence Jones e anormal configurationes electrophoretic in solmente un del casos; (3) leve grados de defectivitate renal; (4) absentia de extense grados de affection skeletal; e (5) absentia de anemia profunde. Omne le tres patientes recipeva prolongate cursos de intense therapia a urethano.

On senti le tentation de attribuer tal prolongate superviventias al effecto del urethano, sed nos debe signalar que urethano ha facite nulle contribution al augmento general del superviventia in myeloma. Ergo il es difficile determinar qual rolo (si ulle rolo del toto) urethano ha habite in le effectuation del superviventia prolongate in iste casos; e nos debe sublinear le possibilitate que certe casos de iste morbo se distingue naturalmente per un curso inusualmente prolongate e relativemente benigne.

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ALVEOLAR-CAPILLARY DIFFUSION DEFECT: A CASE REPORT *

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A group of chronic pulmonary diseases showing diffuse thickening of the alveolar septa has been shown to result in impairment of alveolar-capillary diffusion.[1] The usual example of the syndrome presents with dyspnea, cyanosis, polycythemia and signs of chronic cor pulmonale, yet the partial pressure of carbon dioxide in the arterial blood is normal or low despite serious oxygen desaturation. Various causes for the chronic pulmonary disease responsible for this situation have been noted, including scleroderma, berylliosis, sarcoidosis and silicosis, but most of the cases seem to be cryptogenic pulmonary fibrosis. Reports concerning the effectiveness of adrenocorticotropic hormone in this group of diseases have appeared recently.[2, 3]

Case Report

The patient was 65 years old when admitted to hospital complaining of a chronic, productive cough and dyspnea. The cough had appeared about five years previously, was bothersome chiefly at night, and had progressed to the point of producing one to two cupfuls daily of white, viscid sputum. Dyspnea had appeared about 3 years later and had been rapidly progressive for 1 year. Six months prior to entry he had noted the onset of cyanosis of the nail-beds, ankle edema and, eventually, abdominal swelling. There had been weight loss amounting to 60 pounds during the two years prior to admission. He had become completely incapacitated by the dyspnea.

There had been no previous significant illnesses. The patient had worked for 12 years in an auto body repair shop grinding metal and painted surfaces with flat paper discs coated with silicon carbide. No protective devices were used.

Physical examination showed him to be well developed and well nourished despite the history of recent marked weight loss. He was tachypneic and dyspneic while

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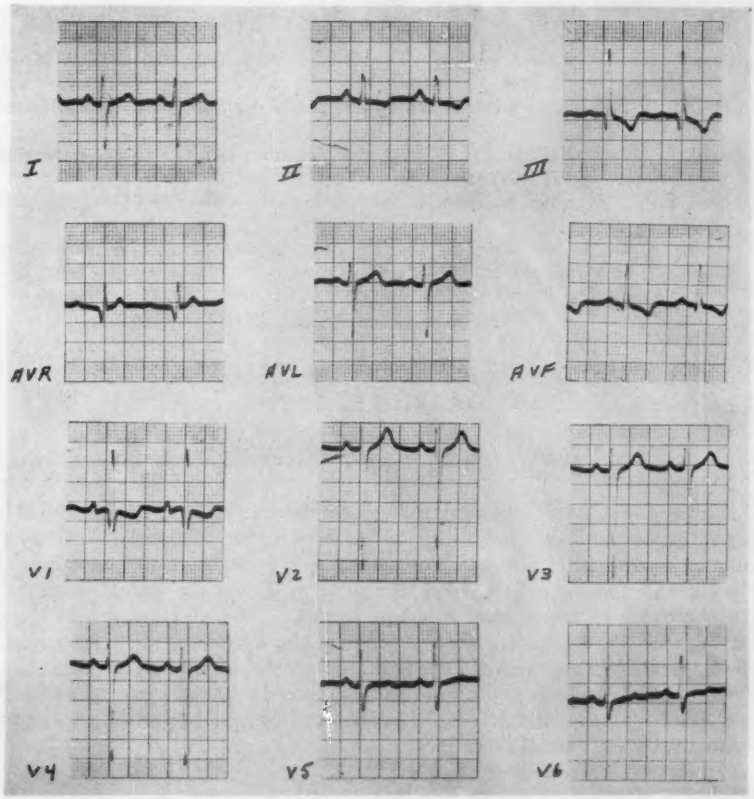


FIG. 1. Electrocardiogram interpreted as showing marked right ventricular hypertrophy.

at rest, breathing about 30 times per minute. There were deep cyanosis of the mucosae and nails and well marked nail clubbing. The blood pressure was normal but a mild tachycardia was evident. The posterior-anterior diameter of the chest was not increased. Respiratory excursions were good and there was no dullness on percussion, but showers of fine, sticky râles were heard at both lung bases posteriorly. The heart did not appear enlarged and no murmurs were heard, but the pulmonary second sound was accentuated. The abdomen was negative, as were also the genitalia and rectum. A trace of pitting edema was present.

Routine laboratory studies showed the urine to be negative. The hemoglobin was 21.2 gm.% and the leukocyte count was 8,400/cu. mm., with 73% polymorphonuclear forms, 20% lymphocytes, 3% monocytes, 3% eosinophils and 1% basophils. The hematocrit was 60% and the sedimentation rate 3 mm./hour. The blood urea nitrogen was 18 mg.% and the chlorides 111 mEq./L. The total serum proteins were 7.5 gm.%, with 3.3 gm. albumin and 4.2 gm. globulin. Sputum smears were negative for acid-fast bacilli, while cultures were positive for coagulase positive staphylococci. The serologic test for syphilis was negative.

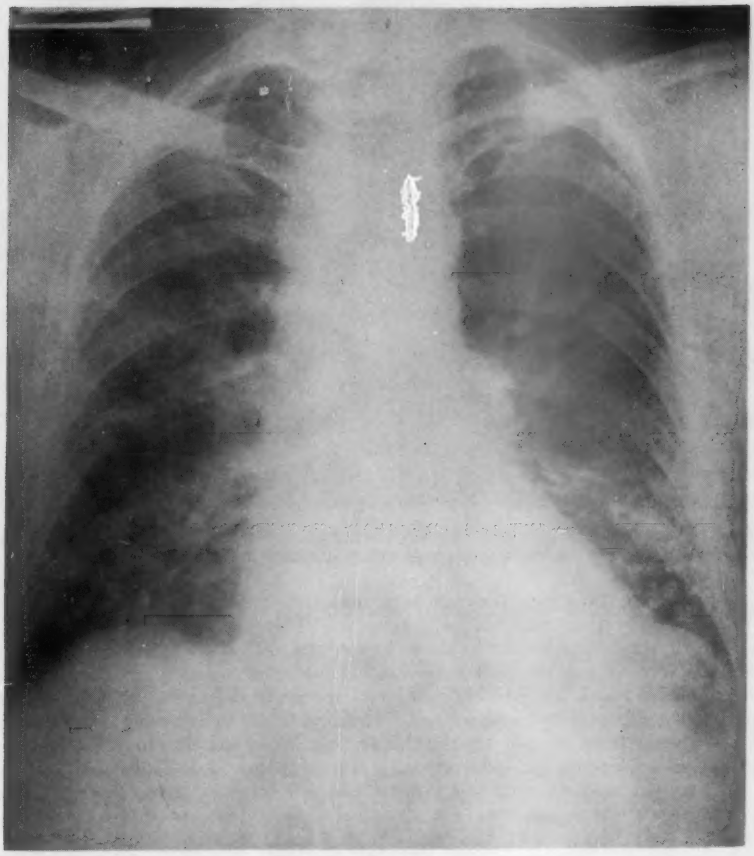


FIG. 2. Chest x-ray showing diffuse pulmonary fibrosis, slight prominence of the pulmonary arteries.

An electrocardiogram (figure 1) showed a right ventricular hypertrophy pattern and a first degree heart block. The heart was of normal size on fluoroscopy but did show evidence of right ventricular hypertrophy. The chest x-ray (figure 2) showed marked diffuse pulmonary fibrosis and also several bullae at the lung bases. The more detailed lung function studies are given in table 1.

In view of recent reports dealing with the use of adrenocorticotropic hormone under similar circumstances, the patient was started on ACTH, 20 mg. intramuscularly four times daily. Aureomycin was given prophylactically, and he also received potassium chloride by mouth. During a period of 17 days no significant change in the clinical state was noted. On the eighteenth day of treatment the patient sat up in bed to cough, became intensely cyanotic, and died almost immediately.

Autopsy Findings: The pertinent findings were limited to the heart and lungs. The heart weighed 580 gm., and the right atrium was considerably dilated. Marked

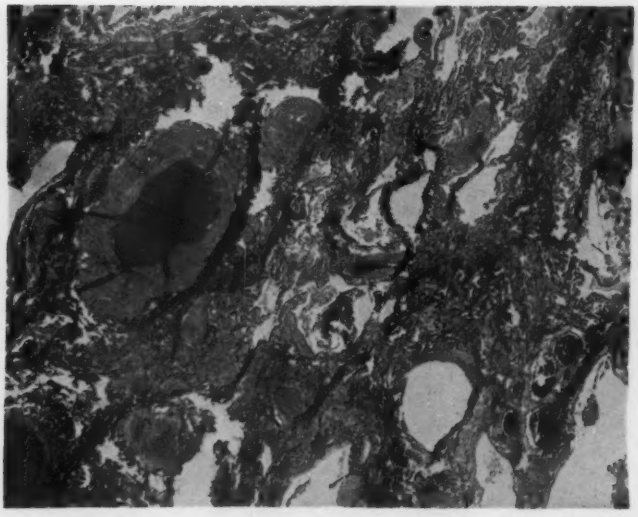


FIG. 3. Photomicrograph of lung showing marked pulmonary fibrosis and medial thickening of the small pulmonary artery branches and arterioles.

hypertrophy of the right ventricle was seen. There was no intracardiac defect. The root of the aorta was unusually sclerotic. The right, left anterior descending, and circumflex coronary arteries showed extensive and severe arteriosclerosis, but at no place was there a complete occlusion. An area of recent infarction measuring 2 by 1.5 by 0.5 cm. involved the posterior surface of the heart near the apex and contained areas of fresh hemorrhage. Scattered areas of scarring were found in the left ventricular muscle and in the septum. Microscopic study confirmed the gross finding of recent posterior myocardial infarction.

The right lung weighed 660 gm. and the left lung 560 gm. The trachea and larger bronchi were reddened and contained yellow purulent material. The pulmonary artery branches were dilated and thickened. Several small emphysematous blebs were seen. The lungs felt rubbery when sectioned, and many single and confluent fibrous nodules were present. The subpleural regions microscopically showed severe fibrotic changes to the extent that normal alveoli could not be found. The changes were not of the concentrically arranged variety with central hyalinization found in silicosis. The capillaries were dilated and the arterioles markedly thickened. There was evidence of acute and chronic inflammatory reaction. The fibrotic changes were less marked in the central portions of the lung, where a few relatively normal alveoli could be seen. In all areas, however, the alveolar septa were much thicker than normal (figure 3).

DISCUSSION

The outstanding findings noted in the laboratory studies are polycythemia, marked arterial oxygen desaturation and a low arterial carbon dioxide content giving a low partial pressure of carbon dioxide. Of the common disorders causing polycythemia and oxygen desaturation in a person of this age, several were excluded by the lung function studies. Normal arterial oxygen values after breathing pure oxygen for seven minutes ruled out a right-to-left shunt

TABLE 1

Laboratory Data

Test	Normal	Patient
Vital capacity	3.4–5.0 L.[4*]	3.1 L.
Arterial O_2 saturation	95–100%	76%
Arterial O_2 saturation after 7 min. of 100% O_2	100–110%	99%
Total lung volume	4340–6730 c.c.[4]	4941 c.c.
Residual air	1430–2390 c.c.[4]	2451 c.c.
Inspiratory reserve	3370 c.c.[4]	1950 c.c.
Expiratory reserve	680 c.c.	590 c.c.
Residual air/total lung volume	25–36%[4]	49%
Alveolar nitrogen (after O_2 washout)	2.5 vol. %	1.9 vol. %
Arterial CO_2 content	25–30 mEq./L.	17.97 mEq./L.
Arterial pH	7.35–7.45	7.40
Arterial pCO_2	40–45 mm. Hg	28.52 mm. Hg

* For males aged 59–66 years.

either in the heart or through a pulmonary arteriovenous fistula. There seemed to be no significant impairment of alveolar ventilation in view of the normal vital capacity, normal washout of alveolar nitrogen, only slightly increased residual lung volume and, most important of all, the normal diffusion of carbon dioxide across the alveolar membrane. The clinical impression of diffuse pulmonary fibrosis without significant pulmonary emphysema was confirmed by the autopsy findings.

It is of some interest that the arterial carbon dioxide tension was actually below the lower limit of normal. It has been observed that if central hypoxic stimulation to respiration is sufficiently strong, hyperventilation in excess of carbon dioxide formation occurs and results in the blowing off of unusually large amounts of the gas and hence lower-than-normal arterial tensions.[5] The basic mechanism allowing impaired diffusion of oxygen and normal diffusion of carbon dioxide between the alveolus and capillary is the much greater diffusibility of CO_2 as compared to O_2, the diffusibility of the former being about 25 times that of the latter across an aqueous membrane.[6] With this in mind, it is not difficult to visualize a situation wherein marked oxygen desaturation and normal or above-normal carbon dioxide elimination may coexist, particularly when diffuse pulmonary disease is present.

The cyanosis in this case was so striking that on initial examination it seemed most likely to be due to a right-to-left intracardiac or intrapulmonary shunt. The possibility of a diffusion defect was not suggested until the more extensive laboratory studies were done. It seems likely that the profound desaturation was of some importance in the death of this patient, ostensibly from severe coronary artery disease.

SUMMARY

1. A case is described of severe diffuse pulmonary disease with marked cyanosis but normal CO_2 elimination.

2. Death was apparently the result of coronary arteriosclerosis.

3. It is not likely that the exposure to silicon carbide was responsible for the pulmonary disease. The pathologic picture was not that of silicosis.

Summario in Interlingua

Es describite un caso de sever cyanosis accompaniate per chronic tusse productive e dyspnea in un homine de 65 annos de etate. Le dyspnea e le tusse habeva essite presente durante circa cinque annos, durante que le cyanosis e le forma hippocratic del lectos de ungula habeva essite presente durante circa sex menses. Le patiente habeva suffrite un marcate perdita de peso. Durante plure annos le patiente habeva essite exponite al pulveres de un officina de reparos de automobiles e habeva usate discos abrasive revestite de carburo de silicium.

Studios laboratorial revelava un nivello hemoglobinic de 21,2 g e un normal numeration leucocytic. Un electrocardiogramma monstrava le configuration de hypertrophia dexteroventricular e de bloco cardiac del prime grado. Le examine roentgenographic del thorace revelava marcate grados de diffuse fibrosis pulmonar.

Extense tests de function pulmonar esseva executate. Il habeva marcate grados de dissaturation arterial de oxygeno, sed le pCO_2 del sanguine arterial esseva infra le norma. Le volumine residue del pulmone esseva normal. Le mesmo valeva pro le volumine total del pulmone. Le nitrogeno alveolar post elution con oxygeno esseva normal. Le saturation arterial de oxygeno montava a 99% post que le patiente habeva respirate 100% de oxygeno durante septe minutas.

Le studios physiologic suggereva un defecto del diffusion alveolo-capillari con marcate obstruction del diffusion de oxygeno sed normal grados de diffusion de CO_2 a transverso le membrana alveolar. Le patiente recipeva un hormon adrenocorticotrophic sed moriva subitemente alicun dies plus tarde, probabilemente in consequentia de insufficientia coronari.

Le necropsia revelava nulle derivation intracardiac o intrapulmonar. Esseva notate sever e extense fibrosis pulmonar sin evidentia significative de emphysema. Marcate grados de arteriosclerosis coronari esseva etiam presente. Le impression clinic de defecto de diffusion alveolo-capillari esseva de accordo con le constatationes autoptic.

Le diffusibilitate de CO_2 a transverso un membrana es circa 25 vices plus grande que illo de oxygeno. Pro iste ration un situation del typo presentate per iste patiente es possibile. Le constatationes pathologic non suggereva que il se tractava hic de un caso de silicosis sed plus tosto de un simple fibrosis pulmonar con marcate alterationes in le arteriolas pulmonar, compatibile con sever hypertension pulmonar.

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5. Altschule, M. D.: Physiology in diseases of the heart and lungs, 1949, Harvard University Press, Cambridge, Mass., p. 76.
6. Riley, R. L.: Pulmonary gas exchange, Am. J. Med. **10**: 210, 1951.

EDITORIAL

CAROTID ARTERY THROMBOSIS

THE syndrome of carotid artery thrombosis has been the subject of numerous recent articles. It is not an uncommon occurrence, having been found in 69 of 3,500 autopsies.[1] Recognition and description of this syndrome has been variously credited but it is apparent that Moniz,[2] in describing the findings in angiography, revived interest in the condition. Previously Hunt,[3] Penzoldt [4] and others had described patients with carotid artery thrombosis and Hunt stressed carotid artery palpation as a means of distinguishing this lesion from other vascular diseases of the brain. The more recent articles have dealt with the clinical features,[5, 6, 7] the pathophysiology,[8, 9, 10] and the treatment.[11, 12]

The syndrome of carotid artery thrombosis, or insufficiency, may present in three different patterns. There is the apoplectic pattern, comprising from 35 to 70% of the cases, depending upon the series examined, in which there is a sudden onset of hemiplegia; there is the pattern of transient episodes of hemiparesis or other evidence of cerebral vascular insufficiency with recovery, which makes up from 30 to 40%; and finally there is the pattern of a progressive neurologic deficit, accounting for from 15 to 25% of the cases. Although there is not complete agreement as to what determines the pattern in a given patient, an important factor is the degree and efficiency

[1] Hultquist, G. T.: Über Thrombose und Embolie der Arteria carotis und hierbei vorkommende Gehirnstörungen, 1942, Gustav Fischer, Jena.

[2] Moniz, E., Lima, A., and de Lacerda, R.: Hemiplegies par thrombose de la carotide interne, Presse med. **45**: 977, 1937.

[3] Hunt, J. R.: The role of the carotid arteries in the causation of vascular lesions of the brain, with remarks on certain special features of the symptomatology, Am. J. M. Sc. **147**: 704, 1914.

[4] Penzoldt, F.: Über Thrombose (autochthone oder embolische) der Carotis, Deutsche Arch. f. klin. Med. **28**: 80, 1880–1881.

[5] Andrell, P. O.: Thrombosis of the internal carotid artery, Acta med. Scandinav. **114**: 336, 1943.

[6] Johnson, H. C., and Walker, A. E.: The angiographic diagnosis of spontaneous thrombosis of the internal and common carotid arteries, J. Neurosurg. **8**: 631, 1951.

[7] Webster, J. E., Gurdjian, E. S., and Martin, F. A.: Carotid artery occlusion, Neurology **6**: 491, 1956.

[8] Fisher, M.: Occlusion of the internal carotid artery, Arch. Neurol. and Psychiat. **65**: 346, 1951.

[9] Millikan, C. H., and Siekert, R. G.: Studies in cerebrovascular disease. IV. The syndrome of intermittent insufficiency of the carotid arterial system, Proc. Staff Meet. Mayo Clin. **30**: 186, 1955.

[10] Meyer, J. S., Leiderman, H., and Denny-Brown, D.: Electroencephalographic study of insufficiency of the basilar and carotid arteries in man, Neurology **6**: 455, 1956.

[11] Millikan, C. H., Siekert, R. G., and Shick, R. M.: Studies in cerebrovascular disease V. The use of anticoagulants in the treatment of intermittent insufficiency of the internal carotid arterial system, Proc. Staff Meet. Mayo Clin. **30**: 578, 1955.

[12] Eastcott, H. H. G., Pickering, G. W., and Rob, C. G.: Reconstruction of the internal carotid artery in a patient with intermittent attacks of hemiplegia, Lancet **2**: 994, 1954.

of the collateral circulation. Thrombosis of the carotid artery would undoubtedly produce grave neurologic deficit were it not for collateral circulation. The most important pathways of collateral circulation are two in number, one communicating with the opposite carotid artery system through the anterior communicating artery and the other communicating with the vertebral artery system via the posterior communicating artery. Other routes for collateral circulation communicate with the external carotid system via the ophthalmic artery, a branch of the internal carotid which connects with various branches of the external carotid, including the angular artery, middle meningeal, and the supraorbital arteries. Not only is the pattern of the syndrome determined by the collateral circulation, but the specific symptoms as well. Most symptoms are those resulting from damage in the distribution of the middle cerebral artery, since the anterior cerebral distribution is more likely to benefit from collateral circulation through the anterior communicating artery.

Location of the occlusion in the intracranial portion of the internal carotid artery may decrease the ophthalmic artery collateral circulation and may result in blindness and optic atrophy. The collateral circulation to the circle of Willis from the external carotid system may also be unfavorably affected. In addition, such an intracranial occlusion may well diminish any circulation from the vertebral-basilar system via the posterior communicating artery.

The most frequent symptoms found in this syndrome, with approximate incidence, are listed:

Hemiplegia or hemiparesis	80%
Aphasia	30 to 60%
Cephalalgia	20 to 50%
Mental disturbance	20%
Hemianesthesia or hemihypesthesia	15%
Unconsciousness	15%
Monoplegia or monoparesis	15%
Visual disturbances	10 to 30%
Paresthesias of one extremity	10%
Seizures	10 to 20%
Homonymous field defect	5 to 12%
Optic atrophy	5 to 10%

The condition appears to be more frequent in males with a 4 to 1 ratio in their favor. It appears also more frequently on the left side in a 3 to 5 ratio. Although most frequent in the fourth, fifth and sixth decades of life, it actually may be encountered in all decades from the second forward.

The differential diagnosis considered in this clinical syndrome will vary with the clinical pattern found in the individual case. The patient who presents with transient episodes may have attacks of headache, paresthesias, aphasia or hemiparesis which may clear gradually or suddenly and often incompletely. Such attacks may persist for months or years, often terminating in a permanent hemiplegia or aphasia. The diagnoses which must be

considered in this instance include multiple thromboses or emboli, tumor with focal seizures, or migraine. The slowly progressive pattern is often steplike in its progression with occasional acute episodes of paresthesias or weaknesses, often in the hand or arm first, later spreading to involve the lower extremity. An expanding intracranial mass is certainly to be considered in such cases.

In the apoplectic form all conditions which may produce a sudden hemiplegia must be considered, including cerebral embolism, hemorrhage, aneurysm, and bleeding tumor, among others.

The most important factor in diagnosis is to keep the syndrome in mind and to remember that it is not uncommon. The presence of monocular blindness with contralateral hemiplegia is almost diagnostic itself. Absence of carotid artery pulsations by palpation is quite helpful but not certain, since some occlusions are intracranial.[13] Palpation may be made in the neck or in the lateral wall of the pharynx.[14] Measurement of the retinal artery pressure has also been found helpful in diagnosis. The retinal artery blood pressures are lower on the affected side in most, but not all cases.[15] It has been noted that in carotid artery occlusion pressure on the affected carotid produces no change in the retinal artery pressures, while pressure on the contralateral carotid produces a drop of retinal artery pressures in both eyes and retinal blanching. Such a maneuver may also produce neurologic symptoms of unconsciousness, seizures, hemiplegia or other deficits. Electroencephalograms are variable, presenting evidence of focal damage on the affected side, diffuse involvement of both hemispheres or no change at all. Compression of the contralateral carotid characteristically produces slowing of the electroencephalogram over the affected hemisphere or both hemispheres. Pneumoencephalography may reveal a normal ventricular system, or dilation of the lateral ventricle on the affected side. Skull x-rays and cerebrospinal fluid findings are usually normal.

The only certain way of making the diagnosis is by means of angiography or surgical exploration of the involved artery. Angiography reveals usually either complete or partial occlusion of the internal carotid artery, just above the bifurcation of the common carotid in approximately 75%. In about 10% of the cases the occlusion is intracranial, affecting the siphon. The remaining cases have occlusion either of the common carotid or common internal and external carotid arteries. It is very common for the anterior cerebral artery of the affected side to fill on injection of the contrast media into the contralateral carotid artery. There may also be reflux of the media

[13] Rosegay, H.: Limited value of carotid pulse in diagnosis of internal carotid thrombosis, Neurology **6**: 143, 1956.

[14] Dunning, H. S.: Detection of occlusion of the internal carotid artery by pharyngeal palpation, J. A. M. A. **152**: 321, 1953.

[15] Thomas, M. H., and Petrohelos, M. A.: Diagnostic significance of retinal artery pressure in internal carotid involvement, Am. J. Ophth. **36**: 335, 1953.

down into the carotid artery of the affected side on injection of the contralateral carotid.[16]

Although the pathologic etiology is usually arteriosclerosis, with normal blood pressure, other causes have been suggested in the literature. These include syphilis, thromboangiitis obliterans, trauma, retrograde thrombosis from a thrombus of one of the cerebral vessels, retrograde thrombosis from a cerebral aneurysm and compression of the internal carotid artery by the lateral process of the atlas.[17] Recanalization of the thrombosis has been described but it is doubtful if such recanalization is ever functionally useful. Various causes for the transient episodes of cerebral anoxia have appeared in the literature. Although this was originally believed to be the result of vasospasm of cerebral and ophthalmic arteries, possibly as a reflex from the diseased carotid artery,[5] more recently other explanations have been advanced. Denny-Brown [10] has produced evidence that such transient symptoms are the result of changes in the degree of collateral circulation which must occur with any fluctuation in blood pressure. He has pointed out the common association of carotid sinus sensitivity with carotid artery thrombosis, and the effect of gravity in producing depression of the blood pressure in patients with carotid artery occlusion. Millikan [11] has suggested that these transient episodes result rather from small soft emboli breaking loose from the carotid artery thrombosis. It has been suggested that such an embolus may temporarily occlude a cerebral vessel which is large enough to produce symptoms and then may continue on its course to a smaller vessel, or may shatter into very small fragments which lodge in such small vessels that few, if any symptoms result.

Treatment of this condition has varied. In an effort to prevent vascular spasm, cervical sympathectomies and arterial stripping have been attempted. This has not resulted in any definite benefit to the patients. Likewise, resections of the affected artery have been performed either to prevent reflex spasm or to remove a source of emboli.[7] This procedure has likewise resulted in no definite benefit and has been criticized as precluding any benefit which might accrue from recanalization. More recently, the use of anticoagulants has been reported to be of benefit in preventing the transient episodes.[11] The dose of Dicumarol was sufficient to maintain the prothrombin time between 30 and 40 seconds (normal 18 to 20 seconds) and produced a cessation of the recurrent episodes. Measures for maintaining collateral circulation by preventing a depression of the blood pressure have included abdominal binders, elastic stockings and avoidance of hypotensive drugs. Ephedrine and atropine may be used to reduce carotid sinus depression. Promising results have been achieved through excision

[16] Vaernut, K.: Collateral ophthalmic artery circulation in thrombotic carotid occlusion, Neurology **4**: 605, 1954.

[17] Baldrey, E., Maass, L., and Miller, E.: The role of atlantoid compression in the etiology of internal carotid thrombosis, J. Neurosurg. **13**: 127, 1956.

of the occluded area of the artery and reconstitution by anastomosis or with arterial grafts. Both successes as well as failures have been reported using this method of treatment.[7, 12, 18]

Carotid artery occlusion is a syndrome which is not infrequent and for which there is apparently developing a mode of effective treatment. The diagnosis, although made with certainty only through angiography or surgical exploration, may very frequently be made clinically without resorting to these measures. Routine palpation of carotid arteries in all "stroke" cases and an awareness of this syndrome will lead to its more frequent diagnosis.

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[18] Denman, F. R., Ehni, G., and Duty, W. S.: Insidious thrombotic occlusion of cervical carotid arteries treated by arterial graft, Surgery **38**: 569, 1955.

REVIEWS

The Morphology of Human Blood Cells. By L. W. Diggs, M.A., M.D., Dorothy Sturm and Ann Bell, B.A. 181 pages; 21 × 28 cm. (loose-leaf). W. B. Saunders Co., Philadelphia. 1956. Price, $12.00.

This is an atlas of the human blood cells which comes to increase the already numerous family of books, the purpose of which is to guide the beginner or the doubtful "expert" in the interpretation of blood films and bone marrow preparations.

The addition is, in our opinion, a useful one. The material represented was mainly painted from the original and this is often an advantage over photographic figures if the artist is able to interpret the "spirit" of the cell, the impression, namely, that a cytologic element gives to the observer at the first glance: the particular hue of the cytoplasm, the shape of the nucleus and the pattern of its chromatin.

The atlas contains plates in which cells of similar morphology are compared and these are of great help in dissolving the doubts that often assail the observer and that the authors wisely foresaw.

The terminology used is the officially accepted one and the most widely used.

In addition to the figures, there is a description of the cells, their families and of their abnormalities which is just long enough to be complete. Sketch and photographs clarify or explain the concepts of the author when needed. The book is valuable not only to students but all physicians interested in the morphologic aspects of hematology.

G. R.

The Diabetic Life, Its Control by Diet and Insulin: A Concise Practical Manual for Practitioners and Patients. 15th Ed. By R. D. Lawrence, M.A., M.D., F.R.C.P. (London). 228 pages; 13.5 × 21 cm. Distributed in the United States and Possessions by Little, Brown and Co., Boston. 1955.

The newest edition of this 30 year old British classic still bears the imprint of its author's forthrightness and personal experience, not only as a clinician and clinical pathologist, but also as a diabetic himself.

Pathologic physiology and hospital procedures are kept to a bare minimum. Instead, the author tries to help the family physicians accomplish the maximum they can by intelligent appraisal and prompt action in their offices and in the homes of their patients. The British general practitioners, for whom this book is primarily intended, practice, apparently, largely outside of hospitals and diagnostic centers. Dr. Lawrence implies, in his introduction to this edition, that, in spite of the aid to be derived from his volume, patients and practitioners need widespread regional clinics where diabetics, in their own geographic areas, can secure the aid of internists, surgeons, nurses, nutritionists, medical social workers, and chiropodists—who are both experienced and interested in their problems.

A note on the plasma acetone test as a means of assessing the significance of ketonuria might be helpful, as would be a comparison of the value of plasma acetone tests with tests for diacetic acid in the urine. In comments on the incidence of diabetes, the author implies that members of the Jewish religion are a race, and in discussing the treatment of diabetic coma he implies that digitalis is good for peripheral vascular collapse. The former indicates disregard of the opinions of anthro-

pologists, workers in a sister science; the latter indicates perhaps only the era of the author's student days. These solecisms should be corrected in future editions of this most admirable volume.

P. F.

A Modern Pilgrim's Progress for Diabetics. By GARFIELD G. DUNCAN, M.D. 222 pages; 12 × 17.5 cm. W. B. Saunders Co., Philadelphia. 1956. Price, $2.50.

Herself a diabetic, a medical social worker on the staff of a diabetic clinic takes little journeys into the lives of her patients. She learns while she teaches, marries one of the residents, and becomes a mother. Each vignette illustrates an important medical, social, and psychological situation frequently encountered in people with diabetes.

Because of the book's uncompromising literacy, physicians will have to appraise the linguistic abilities and comprehension of those to whom they may recommend it. Nursing, dietetic, and medical social instructors will find it a palatable vehicle for their students. Physicians also may profit especially from the latter third of the book in which is outlined with detailed clarity the management of the patient's diabetes by the patient. The glossary has a definition of an internist as distinct from an intern for which alone the book should be worth its price.

P. F.

Vorträge aus dem Gebiet der klinischen Chemie und Cardiologie. By Prof. Dr. L. HEILMEYER. 96 pages; 15.5 × 24 cm. (paper-bound). Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. 1956. Price, kartoniert DM 10.80.

This book represents a series of lectures delivered by Dr. Heilmeyer in medical schools in Munich and in Japan and India.

The first chapter, entitled "Scientific Thought in Medicine as Exemplified by Investigation of the Blood," gives a brief history of the philosophy of the blood from Empedocles to the present time and discusses the factors affecting the sedimentation rate, the electrophoresis pattern of plasma proteins, alcohol fractionation of proteins and the serum properdin concentration and its influence upon the resistance of the animal to experimental infection.

The second chapter, "The Clinical Significance of the Plasma Copper and Plasma Iron Estimations," describes some of the author's work on the relation of the two metals to the experimental administration of various foreign proteins to animals and man. The differentiation between iron deficiency and infectious anemia by serum copper, the differentiation between acute infectious hepatitis and obstructive jaundice by urine copper determination, and the relation between serum copper and phenol oxidase are discussed.

The third chapter is concerned with studies on ferritin. Here a large amount of technical detail is included, and it is clear that the author is quite familiar with his subject.

The fourth chapter describes an apparatus for high voltage electrophoresis of non-protein nitrogenous compounds and gives experimental details. Among the interesting compounds studied is 5 hydroxy-indole-acetic acid, which is discussed in relation to its role in carcinoid.

The fifth chapter describes experimental observations on cardiac physiology by measurement of EKG and cardiac volume (size), and by cardiac catheterization. Studies were made of 2,000 athletes.

The final chapter, "On Mentally Conditioned Changes in the Circulation," describes a number of experiments using provoked anxiety, dreams and hypnosis. Although many EKG records are presented, the author cannot conclude whether the effects are mediated through the cardiac neuromuscular system or the coronary innervation.

This book is an interesting review of the medical research of a single group. It is of little general value, but might be useful to individuals interested in some of the technical details presented.

S. P. B.

Atlas der Phonokardiographie. Optische und magnetische Niederschrift des Herzschalls. Zugleich 2. Auflage der Herzschallregistrierung. By Prof. Dr. ARTHUR WEBER. 236 pages; 15.5 × 23 cm. Verlag von Dr. Dietrich Steinkopff, Darmstadt. 1956. Price, geb. DM 40.–

This is essentially the second edition of "Herzschallregistrierung" (Phonocardiography), published in 1944. It appears shortly after the other German publication, "Atlas of Phonocardiography" by Holldack and Wolff. The text is not materially altered since the first edition. It was much too brief at that time and the improvements have been few. When reviewed against the background of the now already classic monograph of Orias and Braun-Menendez, the superb scholarly text of Calo and the aforementioned atlas of Holldack, the shortcomings of this book are numerous. The discussion of the genesis of heart sounds and murmurs is too brief and too one-sided to be useful. The description of the characteristic auscultatory findings in acquired and congenital heart is inadequate and incomplete. For instance, the character of murmurs and accessory sounds for mitral stenosis is incompletely and in part incorrectly described. In the descriptive part with the presentation of numerous case reports a comparison between auscultatory and phonocardiographic findings is made. Phonocardiography should not be viewed as diagnostic technic but a graphic presentation of sounds for permanent records and teaching.

The graphs are numerous and of varying quality. Some demonstrate the point under discussion very well; others are considerably distorted through an impure baseline.

The shortcomings enumerated above should not distract from the fact that a great deal of interesting information is contained in this monograph. The text is clearly written, the print and reproductions are of excellent quality.

A. G.

The Genesis and Prevention of Cancer. 2nd Ed. By W. SAMPSON HANDLEY, M.S. London, F.R.C.S. 320 pages; 14 × 21.5 cm. The Macmillan Co., New York. 1955. Price, $4.00.

Mr. Handley has painstakingly marshalled a mass of data to support his views on the genesis of cancer. The author takes issue with the present-day irritation theory of cancer causation. The reviewer is impressed with the evidence presented

to support Mr. Handley's conclusion that pre-cancerous lesions are lesions in which the lymphatic vessels have been blocked or obliterated by chronic inflammation or congenital defect. However, despite careful rereading of the significant chapters, the reviewer is still uncertain whether the lymph stasis precedes the pre-cancer or whether the two conditions co-exist, or whether the lymph stasis is the result of the lesion.

Chapter 2, devoted to the lymphatic anatomy of the skin, is excellent. Nowhere else can one find such a concise anatomical description of the skin or one which goes into such detail on the anatomy of skin lymphatics. There are several chapters equally good on lymphatic pathology relative to the lymph stasis as a precursor of cancer, according to the author's views.

It is quickly obvious to the reader that the author has put a great deal of thought and a great amount of effort into this volume. Although the conclusions reached by Mr. Handley have so far not received widespread confirmation, they merit the careful consideration and thought of cancer investigators in all fields.

R. G. C.

Medicina Interna: Compendio Práctico de Patología Médica. 5th Ed. By A. V. Domarus and P. Farreras. 1245 pages; 17 × 26 cm. Manuel Marín y Cia, Barcelona. 1956. Price, $14.00.

This is the fifth edition of this classic Spanish textbook of internal medicine. The various chapters contain descriptions of the pathological entities which are at the same time concise and complete. A brief and useful note of anatomy, physiology and physiopathology precedes some of the most important sections. The therapeutic sections are notable for their description of the most modern drugs and technics.

G. R.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Ageing in Transient Tissues. Ciba Foundation Colloquia on Ageing. Volume 2. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; and Elaine C. P. Millar, A.H.W.C., A.R.I.C. 263 pages; 21 × 14 cm. 1956. Little, Brown and Company, Boston. Price, $6.75.

Behringwerkmitteilungen Begründet von E. v. Behring. Heft 31. Die Schutzimpfung gegen Poliomyelitis (Referate über Arbeiten und Kongresse). Gewidmet dem *5. Deutschen Kongress für ärztliche Fortbildung Berlin vom 23. bis 27. Mai 1956.* 291 pages; 24 × 16 cm. (paper-bound). 1956. N. G. Elwert, Universitäts- und Verlags-Buchhandlung, Marburg/Lahn. Price, DM 3.–

The Biological Effects of Atomic Radiation: A Report to the Public from a Study by the National Academy of Sciences. 40 pages; 28 × 21.5 cm. (paper-bound). 1956. National Academy of Sciences, National Research Council, Washington, D. C. Free distribution in any quantity.

The Biological Effects of Atomic Radiation: Summary Reports from a Study by the National Academy of Sciences. 108 pages; 28 × 21.5 cm. (paper-bound). 1956. National Academy of Sciences, National Research Council, Washington, D. C. Free distribution in any quantity.

Cancer of the Esophagus and the Stomach: A Monograph for the Physician. 2nd Ed. Sixth of a Series on the Early Recognition of Cancer. By OWEN H. WANGENSTEEN, M.D., Professor of Surgery and Head, Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota. 144 pages; 24 × 16 cm. (paper-bound). 1956. American Cancer Society, Inc., New York. No charge.

Cancer of the Lung: An Evaluation of the Problem. Proceedings of the Scientific Session, Annual Meeting, American Cancer Society, Inc., November 3–4, 1953. 322 pages; 26.5 × 20 cm. (paper-bound). 1956. American Cancer Society, Inc., New York.

Clinical Urology for General Practice. By JUSTIN J. CORDONNIER, M.D., F.A.C.S., Professor of Urology, Washington University School of Medicine, St. Louis, Missouri, etc. 252 pages; 25.5 × 17.5 cm. 1956. The C. V. Mosby Company, Saint Louis. Price, $6.75.

Electrocardiographic Test Book (in two volumes). Editor: TRAVIS WINSOR; Advisory and Review Panel: RICHARD ASHMAN, JOSEPH M. BARKER, S. GILBERT BLOUNT, HOWARD B. BURCHELL, J. SCOTT BUTTERWORTH, E. GREY DIMOND, EMANUEL GOLDBERGER, ROBERT P. GRANT, ASHTON GRAYBIEL, HANS H. HECHT, FRANKLIN D. JOHNSTON, ALBERT A. KATTUS, EUGENE LEPESCHKIN, RICHARD H. LYONS, G. W. MANNING, WILLIAM R. MILNOR, GORDON B. MYERS, GERTRUDE NICOLSON, RENO R. PORTER, MYRON PRINZMETAL, FRANCIS F. ROSENBAUM, ERNST SIMONSON, SIDNEY S. SOBIN, MAURICE SOKOLOW, CONGER WILLIAMS, LOUIS WOLFF, PAUL N. YU and ROBERT F. ZIEGLER. 167 pages in Volume I, 132 pages in Volume II; 28.5 × 22 cm. (paper-bound, loose-leaf). 1956. American Heart Association, Inc., New York. Price, $5.00.

Essential Urology. 3d Ed. By FLETCHER H. COLBY, M.D., Consultant, Massachusetts General Hospital, etc. 656 pages; 23.5 × 15.5 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $8.00.

Expert Committee on Biological Standardization: Ninth Report. World Health Organization Technical Report Series No. 108. 20 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30 cents.

Expert Committee on Psychiatric Nursing: First Report. World Health Organization Technical Report Series No. 105. 43 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30 cents.

Handbook of Poisons. By ROBERT H. DREISBACH, M.D., Ph.D., Professor of Pharmacology, Stanford University School of Medicine, San Francisco, California. 426 pages; 18 × 10 cm. (paper-bound). 1955. Lange Medical Publications, Los Altos, California. Price, $3.00.

Internal Secretions of the Pancreas. Ciba Foundation Colloquia on Endocrinology. Volume 9. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and CECILIA M. O'CONNOR, B.Sc. 292 pages; 21 × 14 cm. 1956. Little, Brown and Company, Boston. Price, $7.00.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment. Published with the Approval of the Board of Trustees, American Medical Association. 661 pages; 22.5 × 14 cm. 1956. Intercontinental Medical Book Corporation, with Grune & Stratton, Inc., New York. Price, $5.50.

J. A. M. A. Queries and Minor Notes. 334 pages; 22.5 × 14.5 cm. 1956. Published for the American Medical Association by The C. V. Mosby Company, Saint Louis. Price, $5.50.

Joint FAO/WHO Conference on Food Additives, Geneva, 19–22 September 1955: Report. World Health Organization Technical Report Series No. 107. 16 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30 cents.

Modern Views on the Secretion of Urine: The Cushny Memorial Lectures. Edited by F. R. WINTON, M.A., M.D., D.Sc., Professor of Pharmacology, University College London. 292 pages; 22.5 × 14.5 cm. 1956. Little, Brown and Company, Boston. Price, $8.50.

New Bases of Electrocardiography. Translated from the recent revision of the Third Spanish language edition; copyright by *La Prensa Medica Mexicana,* Mexico 7, D. F. By DEMETRIO SODI-PALLARES, M.D., Chief of the Department of Electrocardiography at the National Institute of Cardiology of Mexico, etc.; with the collaboration of ROYALL M. CALDER, M.D., Editor, English translation, Clinical Professor of Medicine, Graduate School, Baylor University, etc. 727 pages; 25.5 × 17.5 cm. 1956. The C. V. Mosby Company, Saint Louis. Price, $18.50.

Of Water, Salt and Life: An Atlas of Fluid and Electrolyte Balance in Health and Disease. 72 pages; 23.5 × 18 cm. 1956. Lakeside Laboratories, Inc., Milwaukee. Price, $7.50.

Peripheral Vascular Disorders. Edited by PETER MARTIN, V.R.D., M.Chir., F.R.C.S.Ed., Lecturer in Surgery, Postgraduate Medical School, London, etc.; R. BEVERLEY LYNN, M.D., F.R.C.S., Assistant Professor of Surgery and Markle Scholar, Medical College, University of Saskatchewan, etc.; J. HENRY DIBLE, M.B., LL.D., F.R.C.P., Professor Emeritus of Pathology, University of London, etc.; and IAN AIRD, Ch.M., F.R.C.S., Professor of Surgery, University of London, etc. 847 pages; 25.5 × 18 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $20.00.

Pulmonary Emphysema. Edited by ALVAN L. BARACH, M. D., Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons; and HYLAN A. BICKERMAN, M.D., Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons. 545 pages; 23.5 × 15.5 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $10.00.

The Training of Sanitary Engineers: Schools and Programmes in Europe and in the United States. World Health Organization Monograph Series No. 32. By MILIVOJ PETRIK, Ing., M.S., Professor of Sanitary Engineering, University of Zagreb, etc. 151 pages; 24 × 16 cm. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $4.00.

Venereal Diseases: A Survey of Existing Legislation. 44 pages; 24 × 16 cm. (paperbound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 70 cents.

Venous Return. By GERHARD A. BRECHER, M.D., Ph.D., Julius F. Stone Professor of Physiology, Department of Physiology, College of Medicine, The Ohio State University, Columbus, Ohio. 148 pages; 26 × 17.5 cm. 1956. Grune & Stratton, New York. Price, $6.75.

COLLEGE NEWS NOTES

New Life Members

The College acknowledges with pleasure the following Fellow as a new Life Member:

Dr. Milton H. Robbins, Bronx, N. Y.

Gifts to College Library of Publications by Members

The College expresses its appreciation to the following members who have presented autographed copies of their books to the ACP Memorial Library of Publications by Members:

Leon Schiff, M.D., F.A.C.P., Cincinnati, Ohio, *Diseases of the Liver,* published by J. B. Lippincott Company, Philadelphia, Pa., and Montreal, Que., Canada, 1956, Illustrated, 738 pages.

Irvine H. Page, M.D., F.A.C.P., Cleveland, Ohio, *Hypertension, A Manual for Patients With High Blood Pressure,* 2nd Edition, published by Charles C. Thomas, Springfield, Ill., 1956, Illustrated, 109 pages.

Garfield G. Duncan, M.D., F.A.C.P., Philadelphia, Pa., *A Modern Pilgrim's Progress for Diabetics,* published by W. B. Saunders Company, Philadelphia, Pa., 1956, 222 pages.

Esmond R. Long, M.D., M.A.C.P., Pedlar Mills, Va., *A History of the Therapy of Tuberculosis and the Case of Frédéric Chopin,* published by University of Kansas Press, Lawrence, Kans., 1956, 71 pages.

Esmond R. Long, M.D., M.A.C.P., Pedlar Mills, Va., *Tuberculosis in the Army of the United States in World War II,* published by U. S. Government Printing Office, Washington 25, D. C., 1955, 88 pages; Written in collaboration with Seymour Jablon, A.M.

Morris M. Weiss, M.D., F.A.C.P., Louisville, Ky., *Bedside Guide for the Management of the Heart Patient,* published by University of Louisville School of Medicine, Louisville, Ky., 1955, 41 pages.

A Library known as the American College of Physicians Memorial Library of Publications by Members is maintained at College headquarters. Members frequently present autographed copies of their books to the College so that the Library has become a living memorial to those members.

The College would consider it a distinct honor to receive autographed copies of books written by its members. The books are acknowledged in the Annals of Internal Medicine, catalogued and carefully preserved for posterity. The books may be referred to at any time at College headquarters.

Schedule of Coming A.C.P. Regional Meetings

1956

Date	*City*	*Territory*	*Governor and/or Chairman*	*Official Guest*
Dec. 1	Ann Arbor	Michigan	H. Marvin Pollard, M.D.	Chester M. Jones, M.D., 1st Vice President
Dec. 6	Chapel Hill	North Carolina	Elbert L. Persons, M.D. James M. Alexander, M.D., Chairman	Walter L. Palmer, M.D., President
Dec. 8	Nashville, Tenn.	Kentucky-Tennessee	Rudolph H. Kampmeier, M.D., Chairman Sam A. Overstreet, M.D.	Walter L. Palmer, M.D., President

1957

Jan. 18	Philadelphia	Eastern Pennsylvania	Thomas M. McMillan, M.D.	
Jan. 18–19	Colorado Springs	Colorado	C. F. Kemper, M.D. C. Wesley Eisele, M.D., Chairman	Richard A. Kern, M.D., President-Elect
Feb. 9	Wilmington	Delaware	Lemuel C. McGee, M.D., Ward W. Briggs, M.D., Chairman	Richard A. Kern, M.D., President-Elect
Feb. 23	St. Louis	Missouri	Carl V. Moore, M.D.	Walter L. Palmer, M.D., President
Feb. 23–24	Santa Barbara	Southern California	George C. Griffith, M.D., Harry E. Henderson, M.D., Chairman	Howard P. Lewis, M.D., Regent
March 2	Williamsburg	Virginia	Charles M. Caravati, M.D.	Richard A. Kern, M.D., President-Elect
March 15	Topeka	Kansas	William C. Menninger, M.D., Samuel Zelman, M.D., Chairman	Richard A. Kern, M.D., President-Elect

News Notes for the Annals

Members and subscribers to the Annals of Internal Medicine are invited to send in any news items of interest in the field of internal medicine. Information concerning coming events, such as meetings, postgraduate courses, scholarships; or honors, awards, etc., concerning members of the College, should be submitted at least two to three months in advance of publication. News items close on the 10th of the second month preceding publication. Please make such notes in all detail, names, dates, and places. Send them to the News Editor, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

New Dean Appointed

Hahnemann Medical College and Hospital of Philadelphia

Dr. Charles S. Cameron, Scientific and Medical Director of the American Cancer Society, has been appointed Dean of Hahnemann Medical College and Hospital of Philadelphia.

The American College of Physicians Receives Carnation Award

On March 22, 1956 at Los Angeles, the Carnation Company through its Los Angeles General Offices presented the Distinguished Service Award to The American College of Physicians for the year 1956. The Award was received for the College by Dr. Leland Hawkins, F.A.C.P., then Vice President of the College.

Three years ago the Carnation Company launched a program of presenting Distinguished Service Awards to special medical groups for their excellence in promoting the health and well-being of the nation. Presentations of the Award were made in 1954 and 1955, respectively to the American Academy of General Practice for its excellent efforts in improving the continuing-educational standards for the General Practitioner, and to the American Academy of Pediatrics in recognition of their contributions to the reduction of infant mortality and the improvement of child health.

Postgraduate Course on Pulmonary Function

Under the sponsorship of the American Trudeau Society, in coöperation with the Massachusetts Tuberculosis and Health League, Harvard Medical School, Harvard School of Public Health, Boston University School of Medicine and Tufts College Medical School, a Postgraduate Course on Pulmonary Function will be held in the Dowling Amphitheatre of the Boston City Hospital at Boston, Mass., March 25–29, 1957. Dr. Edward J. Welch is Chairman and Dr. Donald S. King, F.A.C.P., is Co-Chairman. A number of Fellows of the College appear on committees and on the Faculty. The matriculation fee will be $75.00. Further details and registration forms can be obtained from Dr. Edward J. Welch, 1101 Beacon St., Brookline, Mass.

Baylor University College of Medicine, Southwestern Poliomyelitis Respiratory Center, and the Jefferson Davis Hospital, in coöperation with the National Foundation for Infantile Paralysis, Inc., announce their fourth postgraduate course for physicians, nurses, medical social service workers, and physical and occupational therapists, to be held February 25 through March 1, 1957.

The course on "Practical Management of Poliomyelitis and Principles of Rehabilitation" will cover complete care of poliomyelitis with emphasis on the severely involved patient, the effective coördination of services and the principles of rehabilitation.

The tuition fee will be $25.00. For further details write to Dr. William A. Spencer, Medical Director, Southwestern Poliomyelitis Respiratory Center, Education Office, 1300 Kenwood Lane, Houston, Texas.

National Tuberculosis Association Fellowships

The Medical Section of the National Tuberculosis Association, the American Trudeau Society, provides a limited number of fellowships to promote the training of clinicians, medical teachers and scientific investigators in the field of tuberculosis and respiratory diseases. Awards are open to citizens of the United States for work within this country.

Candidates holding the degrees of M.D., Ph.D., or Sc.D., are eligible for awards making possible continuation of graduate study in the field of respiratory diseases in an approved hospital or medical center. Such studies may be oriented toward teaching or research. Residency in an approved hospital under such a fellowship will be credited by the American Board of Internal Medicine toward certification in internal medicine and pulmonary diseases.

Each applicant must have the approval of the head of the department under whom he expects to work. All awards are determined by individual circumstances and are paid directly to the Fellow on a quarterly basis. Fellowships are granted for one year. Not more than two renewals will be considered. Fellowship applications must be received by January 1, 1957. Appointments may begin on any date at the convenience of the applicant. Additional information may be obtained by writing to the Director of Medical Education, American Trudeau Society, c/o The Henry Phipps Institute, Seventh and Lombard Sts., Philadelphia 47, Pa.

Trudeau Fellowships

A few fellowships at a higher level of training and award are offered to specially qualified candidates with an M.D. degree who have been assured of a continued teaching or research appointment upon completion of training. Trudeau Fellowships are awarded for one year, but may be renewed up to a total period of four years.

Further particulars concerning fellowships may be obtained upon request from: Director of Medical Education, American Trudeau Society, c/o The Henry Phipps Institute, Seventh and Lombard Sts., Philadelphia 47, Pa.

Dr. Theodore J. Bauer, F.A.C.P., Associate Professor of Bacteriology and Immunology (Preventive Medicine and Public Health), Emory University School of Medicine, has been named Deputy Chief of the Bureau of State Services of the U. S. Department of Health, Education, and Welfare. Dr. Bauer for the past three years has been Chief of the Service's Communicable Disease Center in Atlanta, Ga. He now replaces Dr. LeRoy E. Burney, F.A.C.P., who has recently been appointed Surgeon General of the U. S. Public Health Service.

Dr. John A. Kolmer, F.A.C.P., Professor of Medicine, Temple University School of Medicine and School of Dentistry, was honored on his 70th birthday by a group of friends, colleagues, assistants, and former students. Dr. Kolmer was presented with three volumes containing letters and greetings from his former research associates in Japan and from others in various parts of the United States.

Dr. Charles Weiss, Head of the Department of Microbiology at the Albert Einstein Medical Center, a former student and research associate of Dr. Kolmer, who

served as master of ceremonies, said, in part: "Much as one would like to dwell on your scientific achievements, it is more fitting in this age of anguish and anxiety to emphasize the influence which you have exerted on the personal lives and happiness of your students, associates and colleagues."

Ralph F. Jacox, M.D., F.A.C.P., Associate Professor of Medicine, University of Rochester School of Medicine; David G. Greene, M.D., Dent Professor of Experimental Medicine, University of Buffalo School of Medicine; Andrew Kerr, Jr., M.D., (Associate), Associate Professor of Medicine, State University of New York College of Medicine at Syracuse; A. McG. Harvey, M.D., F.A.C.P., Professor of Medicine and Director of the Department, Johns Hopkins University School of Medicine; and Stephen M. Tenney, M.D., Associate Professor of Pharmacology, University of Buffalo, will be guest speakers for a postgraduate course in cardiovascular diseases to be given at The Rochester General Hospital. The course will be given on Thursday afternoons from 2:00 to 4:00 p.m. on the following dates: October 11, 25, November 1, 15, 29, December 6, 13, 20, 1956; January 10, 17, 24, 31, 1957. Additional information may be obtained by writing to the Chairman of the Postgraduate Educational Committee, Rochester General Hospital, Westside Division, 501 West Main St., Rochester 8, N. Y.

Dr. Robert A. Matthews, F.A.C.P., heretofore Professor of Psychiatry and Head of the Department of Psychiatry and Neurology, Louisiana State University School of Medicine, has been appointed Professor of Psychiatry at Jefferson Medical College of Philadelphia. He has also recently been appointed Commissioner of Mental Health for the State of Pennsylvania.

Dr. Garfield G. Duncan, F.A.C.P., formerly Clinical Professor of Medicine at Jefferson Medical College of Philadelphia, has been promoted to Professor of Clinical Medicine.

Dr. George R. Herrmann, F.A.C.P., Professor of Medicine and Director of Cardiovascular Service, University of Texas Medical Branch, was honored by his former students from the University of Texas Medical Branch with the presentation of a scroll and plaque to commemorate his 25th year as Professor of Medicine.

Dr. Sydenham B. Alexander, (Associate), Clinical Assistant Professor of Medicine, University of North Carolina School of Medicine, has been named Assistant Administrator of the Division of Health Affairs at the University of North Carolina.

A Scholarship Loan Fund is being created at the Tulane University School of Medicine in tribute to the late Dr. Mary Elizabeth Bass, F.A.C.P., Professor of Clinical Medicine Emeritus. The fund is to be known as the Elizabeth Bass Memorial Scholarship Loan Fund. Contributions may be sent to Dr. Georgiana J. von Langermann, 1430 Tulane Ave., New Orleans 12, La.

Dr. Robert E. Switzer, F.A.C.P., heretofore Chief of Psychiatric Services at the United States Naval Hospital, Portsmouth, Va., has joined the Staff of the Department of Child Psychiatry at the Menninger Foundation, Topeka, Kans. Dr. Switzer will have both supervisory and administrative responsibilities in the Department.

Dr. Charles T. Stone, Sr., F.A.C.P., Professor of Internal Medicine and Chairman of the Department of Medicine, University of Texas School of Medicine, has been appointed the new Chairman of the Medical Advisory Board of the National Muscular Dystrophy Research Foundation, Inc.

A new Outpatient Clinic that will provide both diagnostic and therapeutic services for cerebral palsied children has been opened at the new Metropolitan Hospital, 2nd Ave. & 97th St., New York City, and will be operated by the New York Medical College-Metropolitan Medical Center. Dr. Jerome S. Tobis, (Associate), Professor and Director of Physical Medicine and Rehabilitation, New York Medical College, Flower and Fifth Avenue Hospitals, will be in charge of the newly opened Outpatient Clinic.

Dr. Raymond O. Muether, F.A.C.P., Associate Professor of Internal Medicine, St. Louis University School of Medicine, has been appointed President of the Staff of the St. Mary's Group of Hospitals of St. Louis University. Dr. Paul Murphy, F.A.C.P., Associate Professor of Clinical Medicine, St. Louis University School of Medicine, has assumed the duties of Secretary.

Dr. Carl W. Gottschalk, (Associate), Assistant Professor of Medicine at the University of North Carolina, has recently been honored as the recipient of the John Horsley Memorial Prize of the University of Virginia.

Dr. Thomas M. Durant, F.A.C.P., has been promoted to Professor and Head of the Department of Medicine at the Temple University School of Medicine and Hospital. Dr. Durant, a member of the faculty and medical staff since 1936, assumes the chair of medicine formerly occupied by Dr. Richard A. Kern, F.A.C.P., now Emeritus. Dr. Kern is President-Elect of the American College of Physicians. He will continue his private practice in his offices at Temple University Hospital.

Dr. Durant graduated from the University of Michigan Medical School in 1930 and interned at the University Hospital in Ann Arbor. Thereafter he joined the faculty as an Instructor of Internal Medicine. From 1935 to 1936 he served at the Desert Sanitarium in Tucson, Arizona, as an Associate Physician, before joining the Temple University Faculty.

For some years Dr. Durant was a member of The American Board of Internal Medicine. He was the General Chairman of the 36th Annual Session of the College in Philadelphia in 1955. In addition to his Temple University affiliation, he is Visiting Physician, Philadelphia General Hospital; Consultant in Internal Medicine, U. S. Naval Hospital; Consultant in Cardiology, Veterans Administration Hospital; Associate Editor, *American Journal of Medical Sciences;* Member of Editorial Board, *American Heart Journal.*

Dr. Howard R. Bierman, F.A.C.P., has recently been appointed Medical and Scientific Director of the City of Hope Medical Center, Duarte, Calif.

The Society of Honorary Fellows of the Medical Research Institute of the City of Hope has established an annual lecture to be known as the Samuel H. Golter Lecture. The Lecture is to be delivered annually by an eminent authority in the field of medical research, preferably dealing with one of the major diseases with which the City of Hope Medical Center is engaged.

The first Golter Lecture will be delivered November 15, 1956, at 8:00 p.m. at the Ambassador Hotel, Los Angeles, by Dr. William Dameshek, F.A.C.P., Professor of Medicine, Tufts College Medical School (Boston). His subject will be "Current Status of Myeloproliferative Disorders."

William Rottersman, M.D., (Associate), has resigned his position as Assistant Dean of the Menninger School of Psychiatry at Topeka, Kans., and has entered private practice at 340 Boulevard, N.E., Atlanta, Ga.

Dr. Chester S. Keefer, F.A.C.P., Director and Wade Professor of Medicine, Boston University School of Medicine, and Dr. John E. Gordon, F.A.C.P., Professor of Preventive Medicine and Epidemiology, Harvard School of Public Health, gave lectures at the newly opened public lecture series on "Medicine and Social Research" under the sponsorship of the divisions of biological and social sciences and the National Opinion Research Center at the University of Chicago. Their lectures were entitled "Frontiers in Medico-Social Research" and "Epidemiological Approach to the Study of Disease."

Dr. William C. Menninger, F.A.C.P., Governor for Kansas, A.C.P., and General Secretary, the Menninger Foundation, has announced a grant from the Alfred P. Sloan Foundation, Inc. (New York), of $150,000 to the Menninger Foundation in support of the Menninger School of Psychiatry.

The New York Heart Association is planning a one-day conference on "Atherosclerosis and Coronary Heart Disease" to be held at the Waldorf-Astoria, Tuesday, January 15, 1957. Dr. Robert L. Levy, F.A.C.P., Emeritus Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, is Chairman of the committee. Speakers will include: Dr. Paul Dudley White, M.A.C.P., Executive Director, National Advisory Heart Council, and Consultant, National Heart Institute, U. S. Public Health Service; Dr. E. Cowles Andrus, F.A.C.P., Associate Professor of Medicine and Chairman, Joint Committee on Cardiovascular Teaching and Research, Johns Hopkins University School of Medicine; Dr. Herman E. Hilleboe, and Dr. Ancel Keyes. Many other prominent cardiologists and notables in the public health field are also expected to participate.

Additional information may be obtained by writing to the New York Heart Association, 485 Fifth Ave., New York 17, N. Y.

The Chicago Society of Internal Medicine at its Annual Meeting elected Dr. Joseph B. Kirsner, F.A.C.P., Professor of Medicine, University of Chicago, The School of Medicine, President; Dr. Fred D. Ball, Jr., F.A.C.P., Chicago, Vice President; and Dr. Franklin A. Kyser, F.A.C.P., Assistant Professor of Medicine, Northwestern Medical School, Secretary-Treasurer.

Dr. Stewart G. Wolf, Jr., F.A.C.P., Professor and Head of the Department of Medicine, University of Oklahoma School of Medicine; Dr. Eugene A. Stead, Jr., F.A.C.P., Professor of Medicine and Chairman, Department of Medicine, Duke University School of Medicine (Durham, N. C.); and Dr. Noble O. Fowler, F.A.C.P., Assistant Professor of Medicine and Director of Cardiovascular Research, Emory University School of Medicine (Atlanta, Ga.), participated in the Eighth Annual

Meeting and Scientific Sessions of the Georgia Heart Association held September 14–15, at Savannah, Ga. Acting as Moderator during the Sessions was Dr. Charles F. Stone, Jr., F.A.C.P., Assistant Professor of Clinical Medicine, Emory University School of Medicine.

Dr. Paul Dudley White, M.A.C.P., Boston, Mass., Executive Director of the National Advisory Heart Council, and Consultant, National Heart Institute, U. S. Public Health Service, was a speaker at the recent meeting of the American Medical Writers Association held at Chicago, Ill., September 28–29.

Dr. Howard M. Payne, (Associate), Professor of Medicine, Howard University College of Medicine (Washington, D. C.), and Dr. Sol Katz, F.A.C.P., Adjunct Clinical Professor of Medicine, Georgetown University School of Medicine and George Washington University School of Medicine (Washington, D. C.), participated in a scientific session held by the West Virginia Trudeau Society, September 13. Also in attendance at this meeting and acting as Presiding Officer was Dr. Ralph H. Nestmann, (Associate), (Charleston, W. Va.), who is the President of the West Virginia Trudeau Society.

An intensive, two-week course on "Air Pollution" designed for physicians, industrial hygienists, and engineers concerned with the problem of community air pollution will be given by the New York University Postgraduate Medical School from November 26 through December 7, 1956.

The course will review the basic toxicology of the principal air pollutants, micrometeorological factors, the effects of air pollution on agriculture and commerce, and methods for sampling and analysing the various toxic components. Also described will be the sources of air pollution, including power and steam generation, domestic heating, incineration, internal combustion engines, and the chemical industries. Methods of control and the pattern of governmental regulations will be studied.

Tuition for the course, which is to be given in coöperation with the New York University College of Engineering, is $75.00.

Further information may be obtained by writing to the Dean, New York University Postgraduate Medical School, 550 First Ave., New York 16, N. Y.

Dr. David Lehr, F.A.C.P., has been appointed Director of the newly combined Department of Physiology and Pharmacology at New York Medical College, Flower and Fifth Avenue Hospitals. Dr. Lehr is also Professor of Pharmacology and Director of the Department, and Associate Professor of Medicine at this Institution. He has also been recently made a member of the Poison Control Board of the New York City Health Department.

Dr. Isidore Snapper, F.A.C.P., Director of Medicine and Medical Education, Beth-El Hospital, Brooklyn, N. Y., and Dr. Owen H. Wangensteen, Minneapolis, Minn., conducted the Annual Course in Postgraduate Gastroenterology, October 18–20, at the Roosevelt and new Metropolitan Hospital Center in New York. This course is presented yearly following the Convention of the American College of Gastroenterology and is only open to those who have registered in advance.

Dr. George E. Burch, Jr., F.A.C.P., Henderson Professor of Medicine and Chairman of the Department and Director of the Cardiovascular Research Laboratory, Tulane University of Louisiana School of Medicine, will present a course entitled "Electrocardiography," December 3–14, at the Postgraduate School of Medicine of Tulane University School of Medicine.

Dr. James W. Burks, Jr., (Associate), Assistant Professor of Medicine, Tulane University of Louisiana School of Medicine, presented a course in surgical planing for dermatologists, September 13–15, at the Postgraduate School of Medicine of Tulane University School of Medicine.

Dr. W. Edward Chamberlain, F.A.C.P., Professor of Radiology, Temple University School of Medicine, assumed the Presidency of the American Roentgen Ray Society at its Annual Meeting held at Los Angeles, September 25–28.

Dr. C. Wilmer Wirts, F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College of Philadelphia, has been appointed Director of the Postgraduate Institute of the Philadelphia County Medical Society.

Dr. George L. Waldbott, F.A.C.P., Detroit, Mich., participated in the symposium on bronchial asthma at the 4th Congress of Internal Medicine held at Madrid, Spain, September 26. This discussion was entitled "New Trends in the Treatment of Bronchial Asthma." He also presented a paper on "Incipient Chronic Fluoride Intoxication from Drinking Water" before another section of this meeting.

Dr. Francis J. Braceland, F.A.C.P., Psychiatrist-in-Chief, Institute of Living, and Clinical Professor of Psychiatry, Yale University School of Medicine, has been named Chairman of the 1957 National Health Forum. The Forum is to be held at Cincinnati, Ohio, March 20–21, 1957, and is one of an annual series conducted by the National Health Council in behalf of its 51 national organization members.

Dr. Eugene P. Pendergrass, F.A.C.P., Professor of Radiology, University of Pennsylvania School of Medicine, recently took part in a symposium on "Cancer of the Breast" at the Tenth Annual Rocky Mountain Cancer Conference held at Denver, Colo.

Dr. Henry W. Woltman, F.A.C.P., Professor of Neurology, University of Minnesota (Mayo Foundation), retired July 1, after 37 years as a member of the Staff at the Mayo Clinic (Rochester), on which he has been Professor of Neurology since 1931. Dr. Woltman has also served as Chairman of the A.M.A. Section on Nervous and Mental Diseases (1934), and as Secretary of the Section (1931–33).

Brigadier General M. Samuel White, F.A.C.P., USAF (MC), has been named the new Director of Medical Staffing and Education for the Air Force Medical Service in the Office of the Surgeon General USAF, Washington, D. C.

A course in practical electrocardiology will be presented December 3–7, 1956, at Houston, Texas, by Dr. Demetrio Sodi-Pallares, F.A.C.P., Chief Professor of Cardiovascular Clinics, Universidad Nacional Facultad de Medicina, México, and Chief of Department of Electrocardiography, Instituto Nacional de Cardiologiá, under the auspices of the University of Texas Postgraduate School of Medicine and Baylor University College of Medicine.

In addition to Dr. Sodi-Pallares' evening course and his clinical pathological conference discussions, individual instruction in reading electrocardiograms will be provided by faculty members of the sponsoring institutions. For more advanced students, panel discussions will be held on subjects of special interest to electrocardiologists.

Inquiries should be addressed to the University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25, Texas.

Dr. Frank H. Bethell, F.A.C.P., Professor of Internal Medicine and Associate Director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan Medical School, was Chairman of a Symposium on Endocrines and Nutrition held at the University of Michigan (Ann Arbor), October 11–12.

The Symposium was sponsored by the University of Michigan Medical School and the National Vitamin Foundation, a non-profit medical research organization, to discuss the latest reports on research into the mysteries of the endocrine system. The Symposium was part of a continuing program of research in nutrition and related fields supported by the National Vitamin Foundation in coöperation with leading university medical schools and medical research centers. Nearly 200 scientists from all parts of the country participated in the scientific sessions.

Dr. T. Grier Miller, F.A.C.P., Emeritus Professor of Medicine, University of Pennsylvania School of Medicine, and Ex-President of the A.C.P., was the official representative of the College at the Fourth International Congress of Internal Medicine held September 19–23, at Madrid, Spain. In addition to Dr. Miller, many members of the College took active part in the program.

Report of Committee to Review the Functions of the Joint Commission on Accreditation of Hospitals

At the annual meeting of the House of Delegates of the American Medical Association, June 1955, certain resolutions were adopted requesting appointment of a special committee to review the functions of the Joint Commission on Accreditation of Hospitals. This is an abstract of important portions of the report of the said Committee.

History of Accreditation

A hospital standardization program was begun by the American College of Surgeons in 1920, the purpose of which was ". . . to create in the hospital an environment which will assure the best possible care of the patient." The American College of Surgeons conducted this program until December, 1951, when it became too expensive, at which time they proposed to turn it over to the American Hospital Association. The American Medical Association then took definite action and it was agreed that both medical and hospital groups should be represented in the program. On December 15, 1951, the Joint Commission on Accreditation of Hospitals was established.

According to the Bylaws of the Joint Commission on Accreditation of Hospitals, Article IV, Section 1, "The members of this corporation shall be The American College

of Physicians, The American College of Surgeons, The American Hospital Association, and the American Medical Association." A subsequent amendment authorized membership of the Canadian Medical Association.

The Work of the Special Committee

Submitted to the Committee through the House of Delegates by delegates from various parts of the country were many questions about the authority, methods of operation and other relevant details concerning the administration and operation of the Joint Commission. The Committee consulted many individuals at its Executive Session and deliberated long and earnestly on the whole subject, arriving at the following conclusions:

1. Accreditation of hospitals should be continued.
2. The Joint Commission should maintain its present organizational representation.
3. The Board of Trustees should report annually to the House of Delegates on the activities of the Joint Commission.
4. Physicians should be on the administrative bodies of hospitals.
5. General practice sections in hospitals should be encouraged.
6. Staff meetings required by the Joint Commission are acceptable, but attendance requirements should be set up locally and not by the Commission.
7. The Joint Commission should not concern itself with the number of hospital staffs to which a physician may belong.
8. The Joint Commission is not and should not be punitive.
9. The Joint Commission should publicize the method of appeal to hospitals that fail to receive accreditation.
10. Reports on surveys should be sent to both administrator and chief of staff of hospital.
11. Surveyors should be directly employed and supervised by the Joint Commission.
12. Surveyors should work with both administrator and staff.
13. New surveyors should receive better indoctrination.
14. Blue Cross and other associations should be requested not to suspend full benefits to non-accredited hospitals until those so requesting have been inspected.
15. The American Medical Association should conduct an educational campaign for doctors relative to the functions and operations of the Joint Commission.
16. The Committee also suggests that the American Medical Association and the American Hospital Association encourage educational meetings for hospital boards of trustees and administrators either on state or national levels to acquaint these bodies with the functions of accreditation.
17. This Committee asks to be discharged upon submission of this report to the House of Delegates.

Health and Accident Coverage Now Available to Age 75 for A.C.P. Members Currently Insured Under the Original Group Plan (PG-37)

At the 1956 Annual Session, the Board of Regents on the recommendation of the Committee on Insurance approved a plan for continued Health and Accident Coverage of currently insured Members after their protection under the original Health and Accident PG-37 Group Plan terminates as a result of the attainment of age 70.

Under the Original PG-37 Group Plan, protection terminates on the next premium due date following the insured's attainment of age 70. The new Group Plan, to be known as A Conversion Group Disability Plan for Senior Age Members (PG-52), will make possible continued coverage up to age 75. We feel this new PG-52 Group Plan will provide a well-rounded disability insurance program for all Members. We know of no similar plan available at the age of 70 as the one described below.

To be eligible for this new coverage, a Member must be currently insured under the original PG-37 Group Plan, in the active, civilian practice of medicine on the date of application for, and the effective date of, the new PG-52 Group Plan. Application for this Conversion Group Disability Plan must be made within 30 days prior to the termination of coverage under the PG-37 Group Plan on the first premium due date following the Member's 70th birthday. Thereafter, he is not eligible to apply.

If 50% of the Members eligible for the new PG-52 Group Plan as of any October 15th or April 15th due dates apply for this conversion coverage, such applicants will be granted insurance for at least Plan B regardless of their past medical history. If less than 50% apply, all applications will be subject to Company Selection.

The new conversion coverage will be available in Weekly Benefits of $50.00 or $25.00. Each eligible Member may apply for either $50.00 or $25.00 Weekly Benefit subject to the above mentioned conditions.

Plan	Weekly Disability Benefit	Non-Disabling Injury Limit	Annual Cost	Semi-Annual Cost
A	$50.00	$50.00	$75.00	$38.00
B	$25.00	$25.00	$40.00	$20.50

Coverage under this new PG-52 Group Plan will be renewed as long as insured Member is actively engaged in the duties of his profession in which he is insured, remains a member of the American College of Physicians and pays all premiums when due, until the first premium due date after attainment of age 75, at which time coverage will terminate.

A few of the important features under this new PG-52 Group Plan are: (1) World-wide coverage for accidents and illnesses; (2) Coverage as a passenger on a regular scheduled commercial aircraft; (3) House confinement is not required; (4) No reduction in claim benefits because of other insurance covering the same disability; (5) Cost remains the same up to age 75; (6) No restrictive riders or limitation may be applied on any Member by the Company after the Certificate is issued; (7) There is a 31 day grace period; (8) The insured Member shall have the sole right to select his own physician or surgeon, other than himself, and a physician-patient relationship shall be maintained; and (9) An arbitration clause in the event an insured Member is not satisfied with a claims settlement.

Each Member, currently insured under the PG-37 Group Plan at the time of his eligibility for this PG-52 Group Plan, will receive complete information consisting of a descriptive booklet as well as an application form. These items will be mailed in ample time to allow a Member to apply and receive coverage without any lapse of protection. Any inquiries on this new plan should be addressed to the Group Insurance Administrators, 404 South 42nd Street, Philadelphia 4, Pa.

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Dr. George Erick Bell, Sr., F.A.C.P., Wilson, N. C., May 26, 1956
Dr. William Morgan Brace, F.A.C.P., Ann Arbor, Mich., April 23, 1956
Dr. Anton Julius Carlson, M.A.C.P., Chicago, Ill., September 2, 1956
Dr. Arthur Carlisle Christie, F.A.C.P., Crescent City, Fla., June 22, 1956
Col. Walter Paul Davenport, F.A.C.P., (MC), USA, Ret'd, Minneapolis, Minn., July 17, 1956
Dr. LeRoy Bates Duggan, F.A.C.P., Houston, Texas, Date Unknown
Dr. Harry Anthony Durkin, F.A.C.P., Peoria, Ill., May 20, 1956
Dr. Ernest Henry Falconer, F.A.C.P., San Francisco, Calif., August 11, 1956
Dr. Eugene Mabley Lath, (Associate), Rochester, N. Y., May 16, 1956
Dr. John Owsley Manier, F.A.C.P., Nashville, Tenn., September 2, 1956
Capt. Otis Wildman, F.A.C.P., (MC), USN, Ret'd, Washington, D. C., May 14, 1956

The College headquarters at 4200 Pine St., Philadelphia 4, Pa., would appreciate it if members and readers send in notices of the deaths of members promptly, so that suitable obituaries may be prepared and published. Frequently, deaths of members are not reported for several weeks or even months after a member is deceased.

DR. CHARLES JOSEPH BARTLETT

Dr. Charles Joseph Bartlett, F.A.C.P., died March 6, 1956. Born in Sutton, Vermont, December 18, 1864, he went for his education to Yale University, receiving his B.A. degree in 1892, M.A. degree, 1894, and his M.D. degree from Yale University School of Medicine in 1895.

He did postgraduate study at Harvard Medical School, Boston City Hospital, and the University of Leipzig, Germany. He became Assistant Instructor 1895–98; Assistant Professor 1898–1900; Professor of Pathology, 1900–17; and Emeritus Professor of Pathology, 1917, at Yale University School of Medicine.

Dr. Bartlett was Attending Physician, New Haven Hospital, 1908–17; Attending Physician, Grace Hospital, 1918–30; Pathologist, New Haven Hospital, 1900–17, and Grace Hospital, 1921–48. He was also a Pathologist at the Charlotte Hungerford Hospital (Torrington, Conn.) and the Griffin Hospital (Derby, Conn.).

Dr. Bartlett was a member of the American Medical Association; Connecticut State Medical Society; New Haven County Medical Society; New Haven (city) Medical Society; American Association of Pathology and Bacteriology; American Public Health Association; New York Society of Pathologists; American Association of Immunologists; Society of American Bacteriologists; and the American Association for the Advancement of Science. He was a Diplomate of the American Board of Pathology, and in 1931, became a Fellow of the American College of Physicians.

During Dr. Bartlett's medical career he did extensive writing in the field of Pathology, and had many of his articles published in leading medical journals. He was particularly well known for his work as Commissioner of the New Haven Board of Health, and his work in internal medicine and pathology which included membership on the Connecticut Medical Examining Board for 18 years, serving as President of this Board for a portion of that time.

Few physicians are allotted a life span that enables them to see the results of their endeavors as completely as was true with this physician. He is survived by his son, Dr. Marshall K. Bartlett of Boston, Mass., who is a prominent surgeon; a daughter, Mrs. Roger Sherman Foster, and six grandchildren.

JOHN C. LEONARD, M.D., F.A.C.P.,
Governor for Connecticut, A.C.P.

DR. CLIFFORD BREWSTER BRAINARD

Dr. Clifford Brewster Brainard, F.A.C.P., was born April 1, 1874, at Bristol, Connecticut, and died May 7, 1956, at Hartford Hospital. He received his Ph.B. degree in 1894 from Yale University, and his M.D.. degree in 1898 from Yale University School of Medicine. He was Assistant Physician at St. Francis Hospital, 1919–21; Consulting Physician, Bristol Hospital, 1921–56, and Manchester Memorial Hospital, 1920–56; Consulting Gastroenterologist, Sharon Hospital, 1921–56, Hartford Isolation Hospital, 1924–56, Institute of Living, the Neuropsychiatric Institute and Hospital of the Hartford Retreat, 1935–56.

Dr. Brainard was the first Police Surgeon of the Hartford Police Department, and served in that capacity from 1903–07. He devoted much of his time to public health work, and was sponsor of an ordinance providing that Hartford city health appointments be made on the basis of professional qualifications.

He was a member of the Hartford Medical Society and served as Secretary (1907), Secretary-Treasurer (1920), Vice President (1923), and President (1924); Connecticut State Medical Society; American Medical Association; Phi Gamma Delta; and a Fellow (1929), of the American College of Physicians.

During the First World War, he served as a First Lieutenant in the Medical Reserve Corps of the United States Army.

Dr. Brainard was a respected member of his profession and held in the highest esteem by his patients and colleagues. He is survived by his wife, Mrs. Alice T. Brainard, who resides at 10 Mountain View Drive, West Hartford, Connecticut.

JOHN C. LEONARD, M.D., F.A.C.P.,
Governor for Connecticut, A.C.P.

DR. WILLIAM JUEL BRYAN, JR.

Dr. William Juel Bryan, Jr., F.A.C.P., was born February 1, 1896, in Abilene, Texas, and died July 4, 1956, at the Hillcrest Medical Center, Tulsa, Oklahoma. He attended Castle Heights Preparatory School, and later graduated from Washington and Lee University. His medical education was interrupted by World War I in which he served as a first sergeant in the United States Army. After his discharge from the service, he resumed his medical studies at the Baylor University School of Medicine at Dallas, Texas, where he received his M.D. degree in 1921. Dr. Bryan completed an internship and a three year residency in internal medicine at the Church Home and Infirmary of Baltimore, Maryland. In 1925 he entered the practice of medicine in Tulsa, Oklahoma, specializing in internal medicine. Upon several occasions he left his practice to do postgraduate medical study in the New England Deaconess and the Massachusetts General Hospitals, and at the University of Vienna (Vienna, Austria). Dr. Bryan was Chief of Staff at the Hillcrest Memorial Hospital from 1941–46, and a member of the Governing Board of the Hillcrest Medical Center, 1946–56.

He was a member of the Tulsa County Medical Society, Oklahoma State Medical Society, Southern Medical Association, American Medical Association, American Diabetes Association, Fellow of the American Geriatric Society, Diplomate of the American Board of Internal Medicine, and a Fellow (1930) of the American College of Physicians.

Dr. Bryan is survived by his widow, Mrs. Ruth M. Bryan, who resides at 2135 E. 30th Place, Tulsa, Oklahoma, and his three children.

BERT F. KELTZ, M.D., F.A.C.P.,
Governor for Oklahoma, A.C.P.

DR. EDWARD JOSEPH BUXBAUM

Dr. Edward Joseph Buxbaum, F.A.C.P., died March 30, 1956, of a coronary artery disease, at Jamaica, New York. Dr. Buxbaum was born July 12, 1893, at New York City.

He received his M.D. from Union University, Albany Medical College, in 1914. He then did postgraduate training at the New York Postgraduate Hospital and Medical College, and the Jewish Hospital.

He was Director of Laboratories and Pathologist at the Jamaica Hospital, from 1927–56. Dr. Buxbaum was a member of the American Society of Clinical Pathologists; Queens County Medical Society; New York State Medical Society; American Medical Association; New York State Society of Pathologists; and a Fellow (1930), of the American College of Physicians.

Dr. Buxbaum is survived by his widow, Mrs. Theresa Buxbaum, 8711—150th St., Jamaica 2, New York.

His colleagues express sincere regret at the passing of Dr. Buxbaum.

IRVING S. WRIGHT, M.D.,
A.C.P. Governor for Eastern New York

DR. IRA DIXSON

Dr. Ira Dixson, F.A.C.P., died May 16, 1956, at Denver, Colo. Dr. Dixson was born September 4, 1901, at Buffalo, N. Y. He received his A.B. degree in 1923, from Dartmouth College and his M.D. in 1928, from Harvard Medical School, graduating cum laude.

He was House Officer of New England Deaconess Hospital (1927–28), Surgical House Officer, Massachusetts General Hospital (1928–29), and Surgical Fellow at the Lahey Clinic (1930–31). He then became Medical Officer of the Harvard-Australian Expedition (1931–32). Dr. Dixson served on the Staffs of St. Luke's Hospital (Pittsfield), and the Fairview Hospital at Great Barrington (Mass.).

During World War II he served with the U. S. Air Force (MC), (1942–46), and was discharged with the rank of Major. He then moved to Denver where he became recognized as a leading Internist of the City. He served on the Staffs of St. Luke's, General Rose Memorial, Denver General and Porter's Sanitarium Hospitals. Dr. Dixson was also Assistant Instructor and Assistant Clinical Professor of Medicine at the University of Colorado School of Medicine. His last two years were devoted to medicine at the Veterans Hospitals of Albuquerque, N. M., and Denver, Colo.

He was a member of the Berkshire District Medical Society (Mass.); Massachusetts Medical Society; American Medical Association; Alpha Omega Alpha (honorary medical society, Harvard); National Board of Medical Examiners; Medical Society of the City and County of Denver; Colorado State Medical Society; American Heart Association; American Diabetes Association; and a Diplomate, American Board of Internal Medicine. He became a Fellow (1940), and Life Member (1942), of the American College of Physicians.

To his most intimate conferees, Dr. Dixson was a remarkable person who, of his own choice, was not easily known. To the casual he was strange and remote. To the persistent he revealed a wealth of subtle humor, of humanity and humility.

To his patients he was a loyal, dedicated friend who often went to their aid beyond the sacrifices ordinarily expected of a physician. He was devoted to the traditions and ethics of medicine and was vehemently intolerant when he saw them threatened by ignorance and commercialism. A conscientious teacher of medical students, a wise and thorough physician, his unexpected and premature passing is a tragic loss.

Dr. Dixson is survived by his daughter, Miss Mary Dixson, who resides at 3200 E. Alameda Ave., Denver, Colo.

CONSTANTINE F. KEMPERER, M.D., F.A.C.P.,
A.C.P. Governor for Colorado

DR. LAWRENCE GREENMAN

Dr. Lawrence Greenman, (Associate), of Pittsburgh, Pa., died June 20, 1956, of an intracranial tumor at the age of 35 years. He was born March 23, 1921, at New York City, and received his medical education at Yale University School of Medicine, receiving his M.D. degree in 1934. He then took postgraduate training at the Barnes Hospital (St. Louis, Mo.), New Haven Hospital (New Haven, Conn.), and the University of Pittsburgh Medical Center.

Dr. Greenman then became Assistant in Medicine, at Yale University School of Medicine, a post he held from 1944–47, after which he took an appointment at Washington University School of Medicine as Assistant in Medicine, and later became Instructor in Research Medicine, Pittsburgh School of Medicine, 1947–49. He then became Assistant Professor of Research Medicine, University of Pittsburgh School of Medicine, and held this position until the time of his death. He was on the staff of Presbyterian Hospital of Pittsburgh from 1947–56; Attending Physician, Falk Clinic, University of Pittsburgh School of Medicine, 1948–56; Staff, Children's Hospital of Pittsburgh, 1947–56; and Associate Staff, Woman's Hospital.

Dr. Greenman's endeavors in clinical research led him into the field of diabetes and other metabolic diseases, but later his prime interest was that of the rheumatic diseases and their behavior under steroid therapy. His bibliography is extensive and his name appears on fifty-eight published articles, commencing in 1945 with a Case Report of an instance of streptococcus bacteremia and meningitis cured with penicillin. Thereafter, the wide interest in the problems of internal medicine in general are evident in the titles of the various papers listed.

Dr. Greenman was a member of the Allegheny County Medical Society; Pennsylvania State Medical Society; American Diabetes Association; Clinical Society of Pittsburgh Diabetes Association; Society of Biological Research, University of Pittsburgh School of Medicine; Society of Sigma Xi; American Federation for Clinical Research; American Medical Association; and a Diplomate of the American Board of Internal Medicine. In 1953 he became an Associate of the American College of Physicians.

Dr. Greenman was known to all of us as a very serious and dedicated individual with a searching and analytical mind. To know him was to admire him for his devotion to his duties. All of us at the University have indeed experienced a great loss.

He is survived by his widow, Mrs. Jean H. Greenman, 210 Park Place, Pittsburgh 9, Pa., and his three children.

FRANK J. GREGG, M.D., F.A.C.P.,
Governor for Western Pennsylvania, A.C.P.

DR. ELMER E. HIGHBERGER, JR.

Dr. Elmer E. Highberger, Jr., F.A.C.P., of Greensburg, Pa., died July 28, 1956, at the age of 51 years. He was born at Greensburg, Pa., November 15, 1904. He attended Franklin and Marshall College, receiving his A.B. degree in 1922, and spent

one year at Columbia University. He then enrolled at Johns Hopkins Medical School where he received his M.D. degree in 1930. Dr. Highberger was a House-officer at Baltimore City Hospitals for three years, and was Chief Resident Physician at West Penn Hospital for one year. He later pursued postgraduate work at Ray Brook State Sanatorium, Ray Brook, N. Y., and the Trudeau Sanatorium where he became associated with the late Dr. Lawrason Brown at Saranac Lake, N. Y.

Dr. Highberger served as Instructor in Medicine, at Johns Hopkins University School of Medicine from 1931–33, and Assistant Resident and Resident in Internal Medicine, at Baltimore City Hospitals, 1931–33. He then joined the staffs of the Western Pennsylvania Hospital as a member of the Junior Medical Staff, 1934, remaining until May, 1955. He was Medical Director of the Grand View Institution (Oil City), 1937–39; Member of the Senior Medical Staff, Oil City Hospital, 1937–39; and at one time Chief of the Pneumothorax Clinic (Westmoreland County), and member of the Senior Medical Staff and Cardiologist, Westmoreland Hospital.

Dr. Highberger was instrumental in establishing the Pneumothorax Clinic for Tuberculosis in the area and also established the Rheumatic Fever Clinic in which he served as Chief until his death. He was President of the Westmoreland County Unit of the American Cancer Society and became the first President of the fund when it became the Westmoreland County Cancer Society. He was past President of the Westmoreland Hospital Staff and past President of the Westmoreland County Medical Society.

Dr. Highberger was a member of the American Medical Association; Westmoreland County Medical Society; Fellow, of the American College of Cardiology; American Trudeau Society; Western Pennsylvania Heart Association; American Heart Association; Johns Hopkins Medical and Surgical Association; and past Director of the Westmoreland Public Health Association. He was a Diplomate of the American Board of Internal Medicine, and became a Fellow in 1940 of the American College of Physicians. He was also a Fellow of the American College of Chest Physicians.

Dr. Highberger was author of many medical papers and invented one of the first portable pneumothorax machines.

Dr. Highberger is survived by his mother and his widow, Margaret L. Highberger, a daughter, Gretchen, and a son, Eric; also a brother, Dr. Edgar Highberger; and a sister, Miss Mary Highberger, who lives at home.

FRANK J. GREGG, M.D., F.A.C.P.,
Governor for Western Pennsylvania, A.C.P.

DR. ALFRED MARTIN WOLFE, SR.

Dr. Alfred Martin Wolfe, Sr., F.A.C.P., died March 6, 1956 in San Luis Obispo, Calif. Dr. Wolfe was born in Colorado, April 12, 1904. He received his B.A. degree from the University of Colorado in 1927 and his M.D. degree from the University of Colorado School of Medicine in 1929. He served his internship at St. Luke's Hospital, Denver, and St. Vincent's Hospital, Portland, Ore.

Dr. Wolfe was Physician to the Out-Patient Department, University of Colorado School of Medicine from 1932 and a member of the Staff of the French Clinic, San Luis Obispo. He was Head of the Active Staff, Denver General Hospital since 1935, Lecturer, Central School of Nursing (Denver), since 1933, and Denver General Hospital Training School since 1938; all of the positions were held until his death. During World War II Dr. Wolfe served as a Commander with the U. S. Navy Medical Corps. During Dr. Wolfe's medical career he wrote many articles concerned with his primary field and had them published in various medical journals.

Dr. Wolfe was a Diplomate of the American Board of Internal Medicine and held memberships in the Alameda County Medical Association; California Society

of Internal Medicine; American Heart Association; Heart Division, Alameda County Tuberculosis Medical Association; American Society of City and County of Denver, Colorado State Medical Society, and Fellow (1941) of the American College of Physicians.

Dr. Wolfe was dearly beloved by his patients and also held in high esteem by his fellow practitioners in the San Luis Obispo area. He was an outstanding internist and a leader in this field both in his community and throughout the state. Dr. Wolfe's influence in California will be greatly missed.

He is survived by his wife, Mrs. Helen F. Wolfe, 1367 Mill Street, San Luis Obispo, California, two sons, Anthony Wolfe, Stanford University, and A. M. Wolfe, Jr., California Polytechnic College, his mother, Mrs. Jane Wolfe, Portland, Oregon, one sister, Mrs. J. Gorman Hogan, Portland, Oregon, and one brother, Roy E. Wolfe, M.D., of Boulder, Colorado.

GEORGE C. GRIFFITH, M.D., F.A.C.P.,
Governor for Southern California, A.C.P.

DR. JOHN OLEN WOODS

Dr. John Olen Woods, F.A.C.P., New Castle, Pa., died February 17, following a cerebral vascular accident. Dr. Woods was born in Malvern, Ohio, May 24, 1896. He received his pre-medical education at Mount Union College, and then attended the University of Pittsburgh School of Medicine, where he received his M.D. degree, in 1920. After a brief period in Pittsburgh, as an Associate of the late Dr. John A. Lichty, F.A.C.P., Dr. Woods settled in New Castle, Pa., where he continued to practice until his death.

Dr. Woods' primary interest was in the field of Internal Medicine. He was a member of the Medical Staff of New Castle Hospital, from 1943–56, and Medical Director of the Rheumatic Fever Clinic of the Pennsylvania State Department of Health, from 1948–56.

He was a member of the Medical Society of the State of Pennsylvania, American Medical Association, and the American Heart Association. He was President, (1936) Lawrence County Medical Society, Diplomate, American Board of Internal Medicine, and a Fellow (1938) of the American College of Physicians.

Dr. Woods is survived by his wife, Mrs. Marguerite K. Woods, of New Castle, Pa., and two children, Barbara Woods Rimer, residing in Cleveland, Ohio, and Dr. John O. Woods, Jr., who maintains a practice in Pittsburgh, Pa.

FRANK J. GREGG, M.D., F.A.C.P.,
Governor for Western Pennsylvania, A.C.P.

A RESEARCH MILESTONE

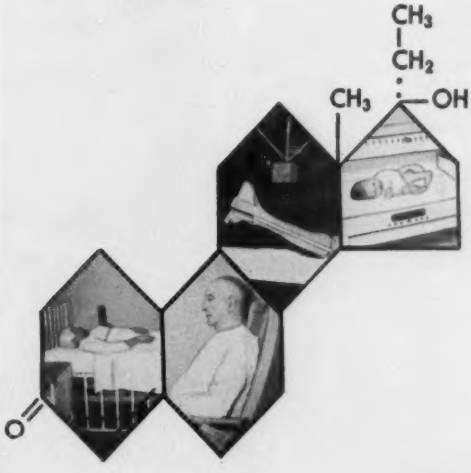
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Searle's New and Practical Steroid Specifically for Protein Tissue Building

It has long been recognized that a substance which would promote protein anabolism would be of inestimable value in therapy. The androgens have this property, but unfortunately they also exert actions on secondary sex characteristics. These effects are commonly undesirable in therapeutic programs.

THE FIRST STEROID WITH ANABOLIC SPECIFICITY—Nilevar, the newest Searle Research development, therefore, meets a long desired clinical need because Nilevar presents the first steroid primarily anabolic for protein synthesis. Moreover, Nilevar is without prominent androgenic effects (only about one-sixteenth of that exerted by the androgens).



OBJECTIVE AND SUBJECTIVE RESPONSE—Orally effective, Nilevar therapy is characterized by retention of nitrogen, potassium, phosphorus and other electrolytes in ratios indicative of protein anabolism. Moreover, subjectively the patient observes an increase in appetite and sense of well-being.

WELL TOLERATED—Nilevar has an extremely low toxicity. Laboratory animals fail to show toxic effects after six months of continuous administration of high dosages. Nilevar should not be administered to patients with prostatic carcinoma. Nausea or edema may be encountered infrequently. Slight androgenicity may be evidenced on high dosage or in particularly responsive individuals.

MAJOR INDICATIONS—Preparation for and recovery from surgery; supportive treatment of serious illnesses (pneumonia, poliomyelitis, carcinomatosis, tuberculosis); recovery from severe trauma and burns; decubitus ulcers; care of premature infants.

DOSAGE—The daily *adult* dose is three to five Nilevar tablets (30 to 50 mg.) but up to 100 mg. may be administered. For *children* the average daily dose is 1 to 1.5 mg. per kilogram of body weight; individual dosages depend on need and response to therapy.

SUPPLY—Nilevar is available in uncoated, unscored tablets of 10 mg. G. D. Searle & Co., Research in the Service of Medicine.

*Trademark of G. D. Searle & Co.

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FRANK J. GREGG, M.D., F.A.C.P.,
Governor for Western Pennsylvania, A.C.P.

A RESEARCH MILESTONE

Nilevar*

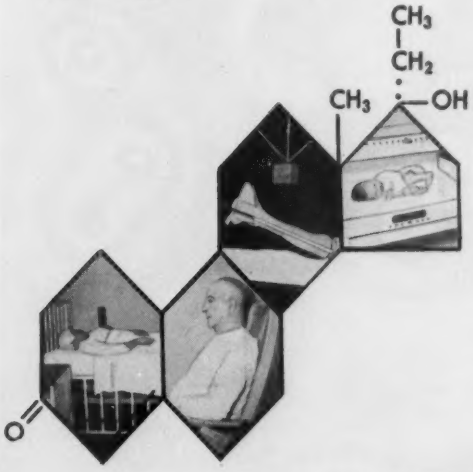
(BRAND OF NORETHANDROLONE)

Searle's New and Practical Steroid

Specifically for Protein Tissue Building

It has long been recognized that a substance which would promote protein anabolism would be of inestimable value in therapy. The androgens have this property, but unfortunately they also exert actions on secondary sex characteristics. These effects are commonly undesirable in therapeutic programs.

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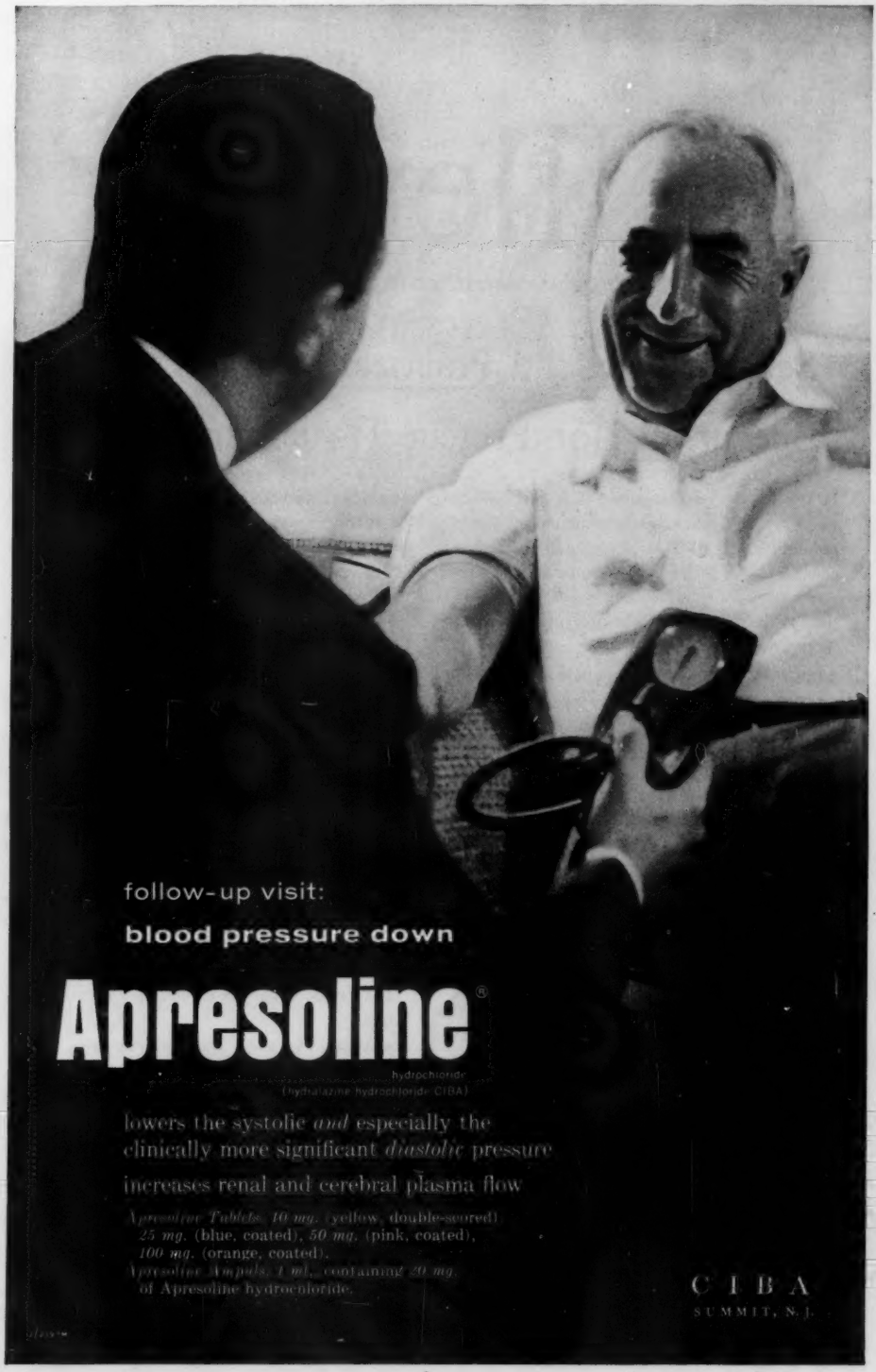
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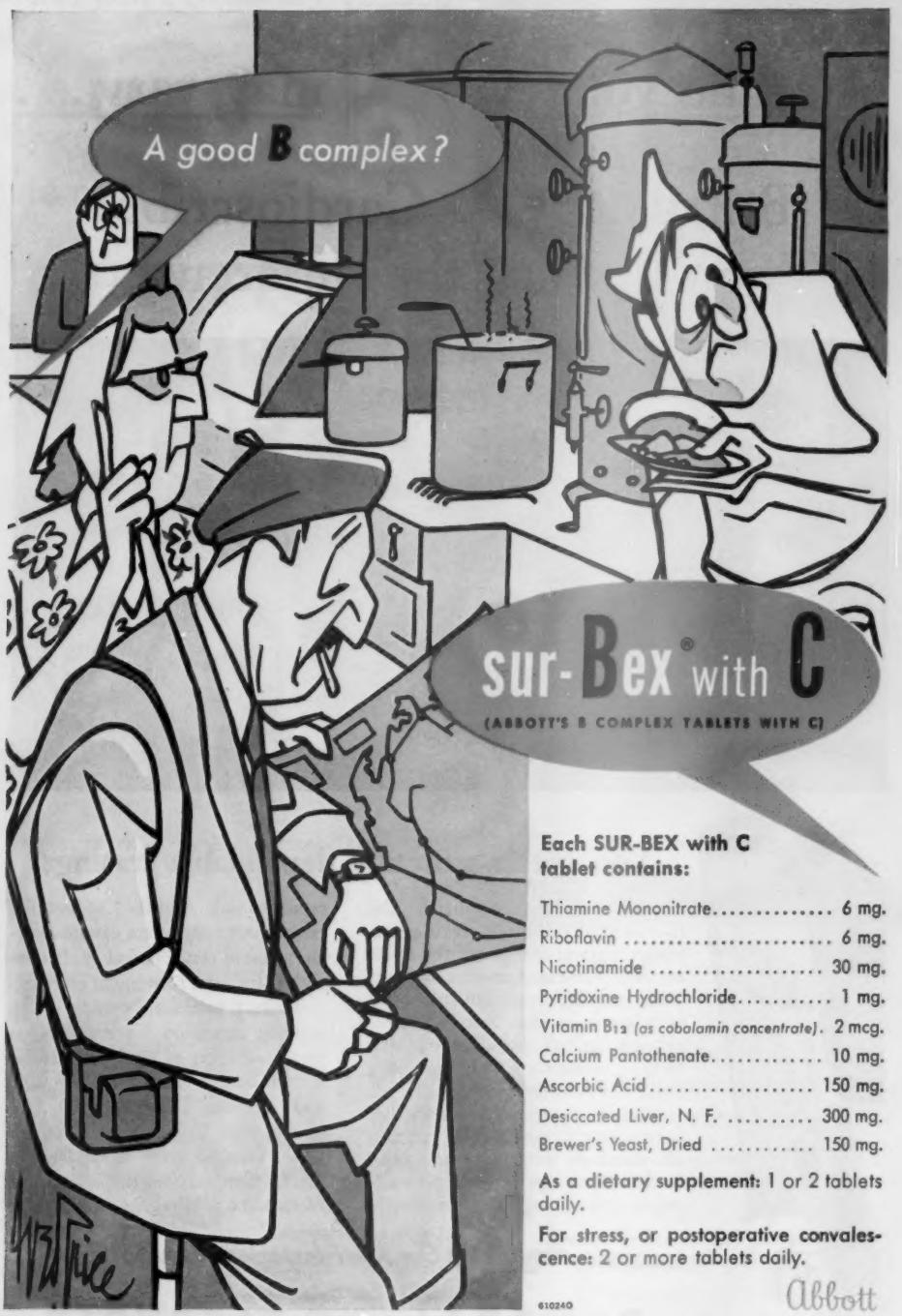
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SUPPLY—Nilevar is available in uncoated, unscored tablets of 10 mg. G. D. Searle & Co., Research in the Service of Medicine.

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Pyridoxine Hydrochloride..... 1 mg.
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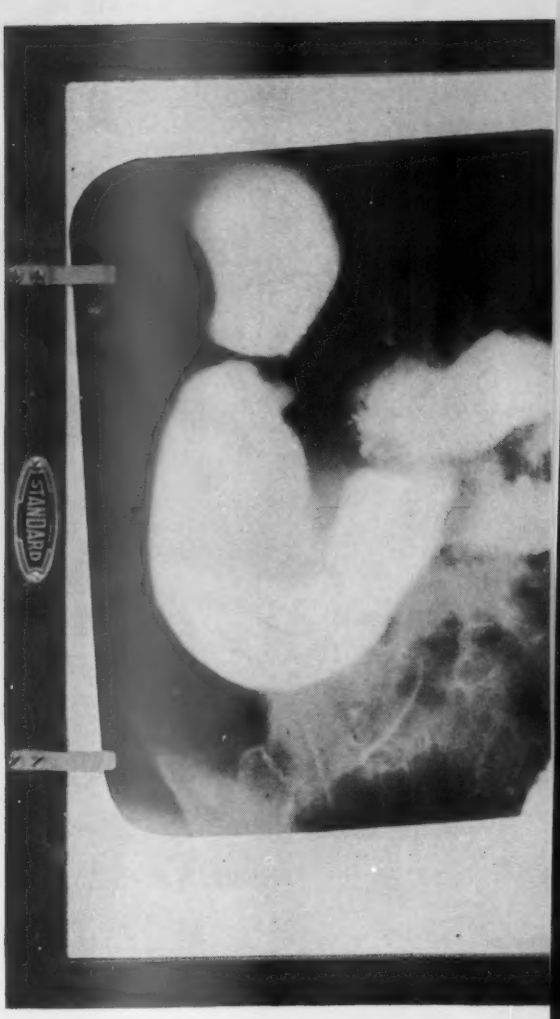
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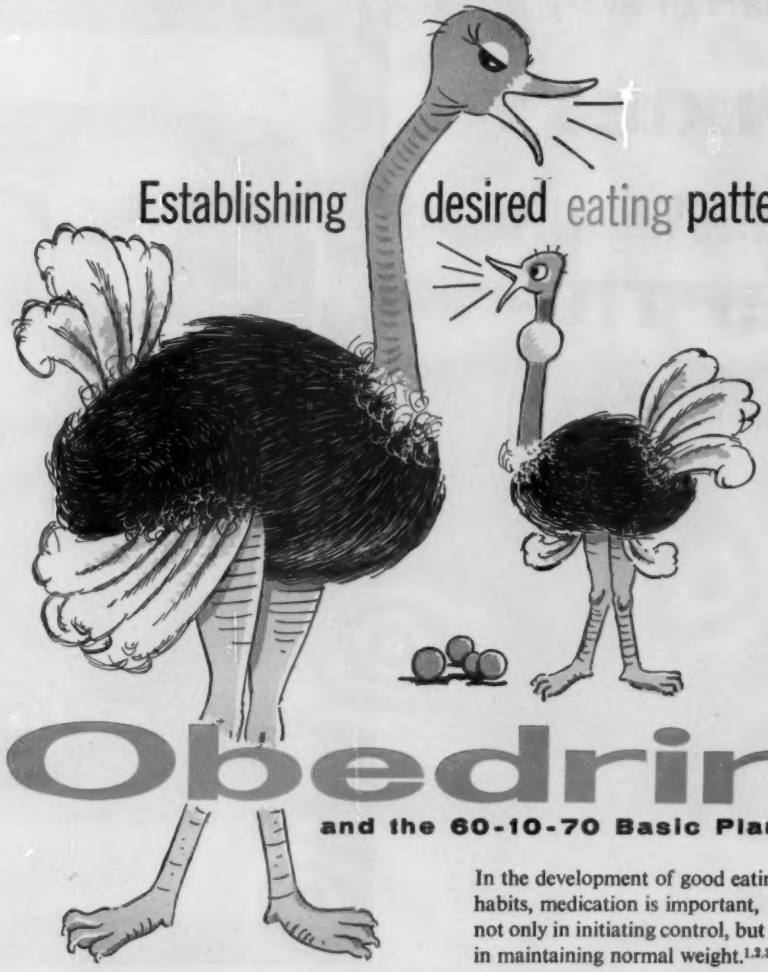
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- Pentobarbital as a balancing agent, to guard against excitation.
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- Ascorbic acid to aid in the mobilization of tissue fluids.

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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

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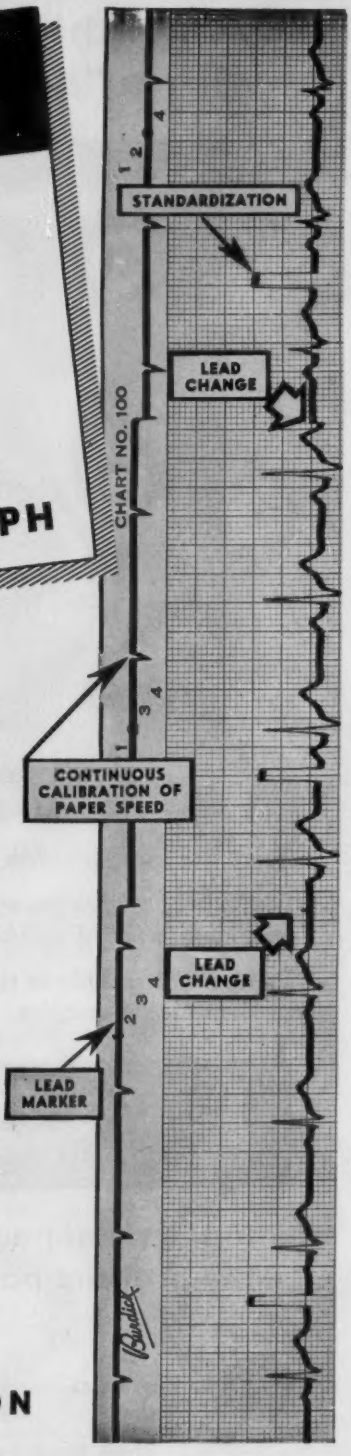
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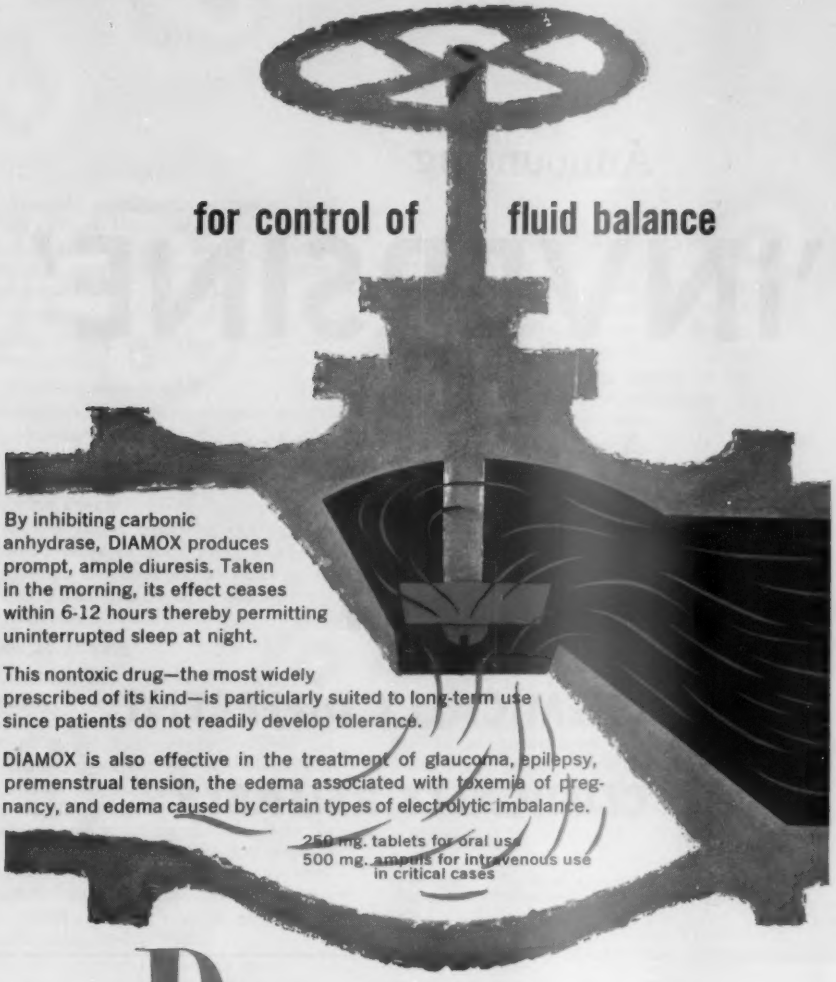


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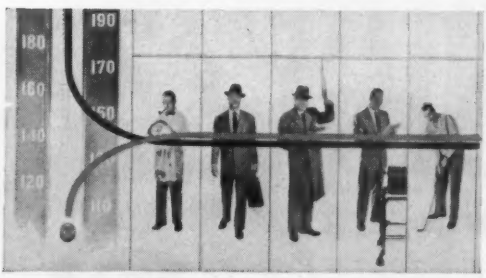
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'INVERSINE,' a secondary amine, is a new and extremely potent antihypertensive agent. It is totally unlike the poorly and erratically absorbed ganglionic blockers of the quaternary ammonium type and has the following clinically demonstrated properties:

1. *Excellent reproducibility* of effects.
2. *Most potent* of all available oral ganglionic blockers (10 to 20 times more potent than pentolinium and about 90 times more potent than hexamethonium).

3. *Smooth, predictable response:* In a given patient, the same dose of 'INVERSINE' elicits the same blood pressure response, time after time, *with minimal day-to-day fluctuation.*

4. *Remarkable physiologic economy* resulting *in long duration of action, sustained* effect.

5. *Gradual* onset of effect.

6. *Small oral dosage* produces required hypotensive effect.

7. *Effective* even in patients refractory to hexamethonium and other ganglionic blocking agents.

In all these respects, 'INVERSINE' differs greatly from all other available ganglionic blocking agents and is, in effect, in a unique category among antihypertensives.

CLINICAL STUDIES

'INVERSINE' has been used by many investigators on thousands of patients. In all this clinical work, this new and very potent agent has amply fulfilled its laboratory promise. By demonstrating reproducibility, high potency and smooth effectiveness with minimal fluctuation – all resulting directly from its complete absorption from the gastrointestinal tract – 'INVERSINE' has successfully circumvented many of the objections to the use of ganglionic blockade in hypertension.

In the opinion of one reviewer ". . . the most useful ganglionic blocking agent to be introduced is mecamylamine ('INVERSINE'). . . . This drug is completely absorbed when given by mouth and has such a gradual onset and offset of action that a continuous and effective level of blockade can readily be achieved. . . ."[1]

Further, in one of many clinical trials,† "The over-all response rate was 92%, and 24% of the patients became normotensive."[2] Investigators have found 'INVERSINE' to be ". . . the most potent and effective of the three drugs in reducing the blood pressure. . . ." ['INVERSINE' and two other ganglionic blocking agents.][2]

Moreover, following ganglionic blockade with 'INVERSINE,' some patients with hypertension may experience relief of pre-existing headache and angina pectoris. Many patients with retinopathy, congestive heart failure and electrocardiographic abnormalities, have shown signs of improvement during treatment with 'INVERSINE.'

'INVERSINE' was thus shown to be most valuable in the management of hypertensive vascular disease.

SIDE EFFECTS

'INVERSINE' (mecamylamine), though comparatively nontoxic, is a very potent agent which must be used with care. Side effects observed during clinical use are due to excessive pharmacologic action. They may be minimized by careful adjustment of dosage and close supervision of the patient.

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Judged by any standard 'INVERSINE' (mecamylamine) is the most satisfactory agent in the treatment of hypertension by ganglionic blockade. It is the most potent and most reliable oral agent for the management of hypertension.

References:

1. Sturgis, C. C., et al.: Advances in Internal Medicine, J. Michigan M. Soc. *55*:154 (Feb.) 1956.

2. Moyer, J. H. et al.: Drug Therapy of Hypertension: Preliminary Observations on the Clinical Use of Mecamylamine (A Ganglionic Blocking Agent) in Combination with Rauwolfia for the Treatment of Hypertension, Med. Rec. & Ann. *49*:390 (Sept.) 1955.

† In this clinical trial all patients were given, in addition to one of the ganglionic blocking agents, a constant daily amount of reserpine.

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1. Balfour, D. C., Jr.: Am. J. Gastroenterol. 22:181, 1954. 2. Burke, J. O., et al.: Internat. Rec. Med. & Gen. Practice Clin. 167:587, 1954. 3. Sternberg, S. D., and Greenblatt, I. J.: Ann. Allergy 9:190, 1951.

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References: 1. Galambos, A.: Angiology 5:449 (Oct.) 1954; 2. Leake, C.D.: Ohio State M.J. 52:369 (April) 1956; 3. Moyer, J.H. et al.: A.M.A. Arch. Int. Med. 96:530 (Oct.) 1955.

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1. Blank, P., and Boas, H.: Ann. West. Med. & Surg. 6:376, 1952.
2. Piper, C. E., and Nicklas, F. W.: Indust. Med. 23:510, 1954.

*U.S. Pat. 2,628,165

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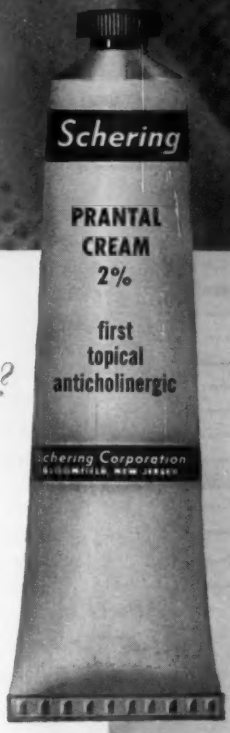
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Formula: Each tablet contains 2 mg. of purified Rauwolfia serpentina alkaloids (alseroxylon fraction).

Dosage: For the first 20 to 30 days, 2 tablets once daily, preferably on retiring; thereafter, the maintenance dose of 1 tablet daily suffices for most patients.

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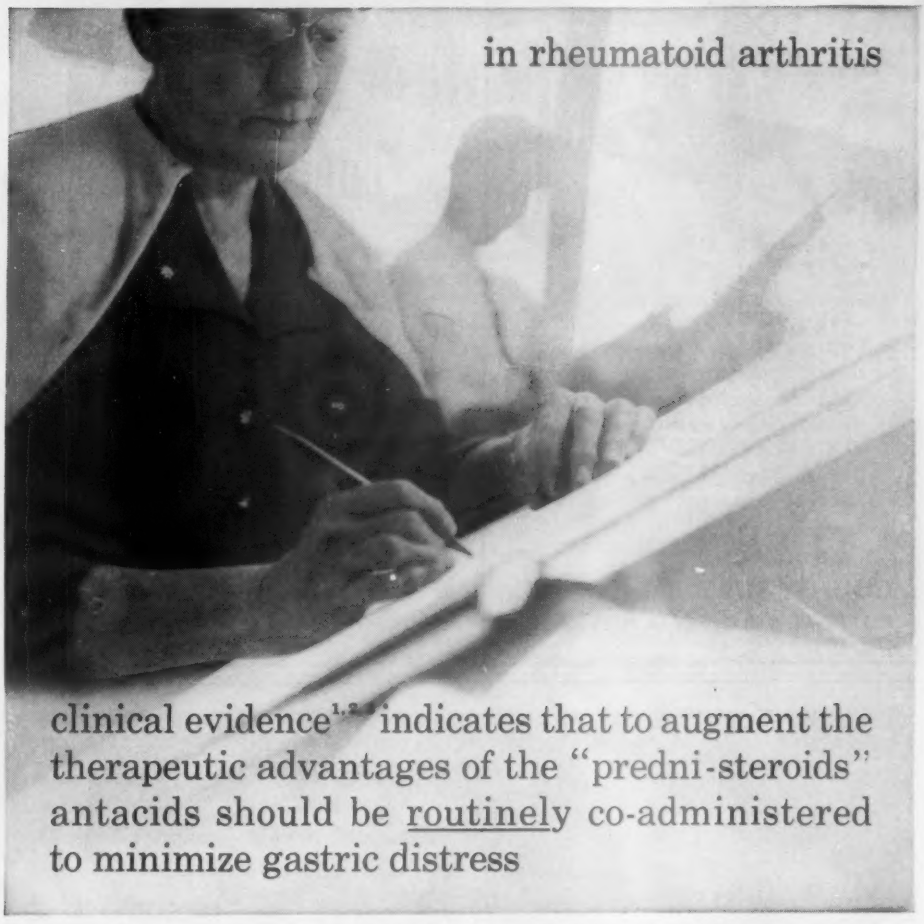
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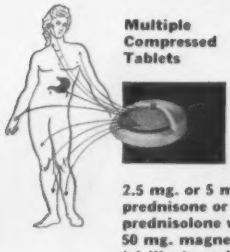
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References: 1. Boland, E. W., *J.A.M.A.* **160**:613 (February 25) 1956. 2. Margolis, H. M. *et al.*, *J.A.M.A.* **158**:454 (June 11) 1955. 3. Bollet, A. J. *et al.*, *J.A.M.A.* **158**:459 (June 11) 1955.

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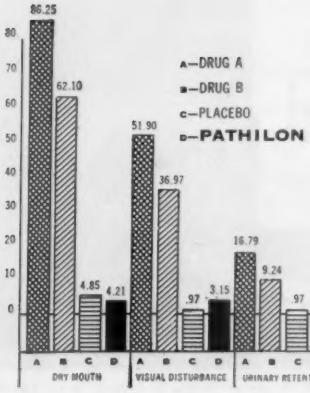
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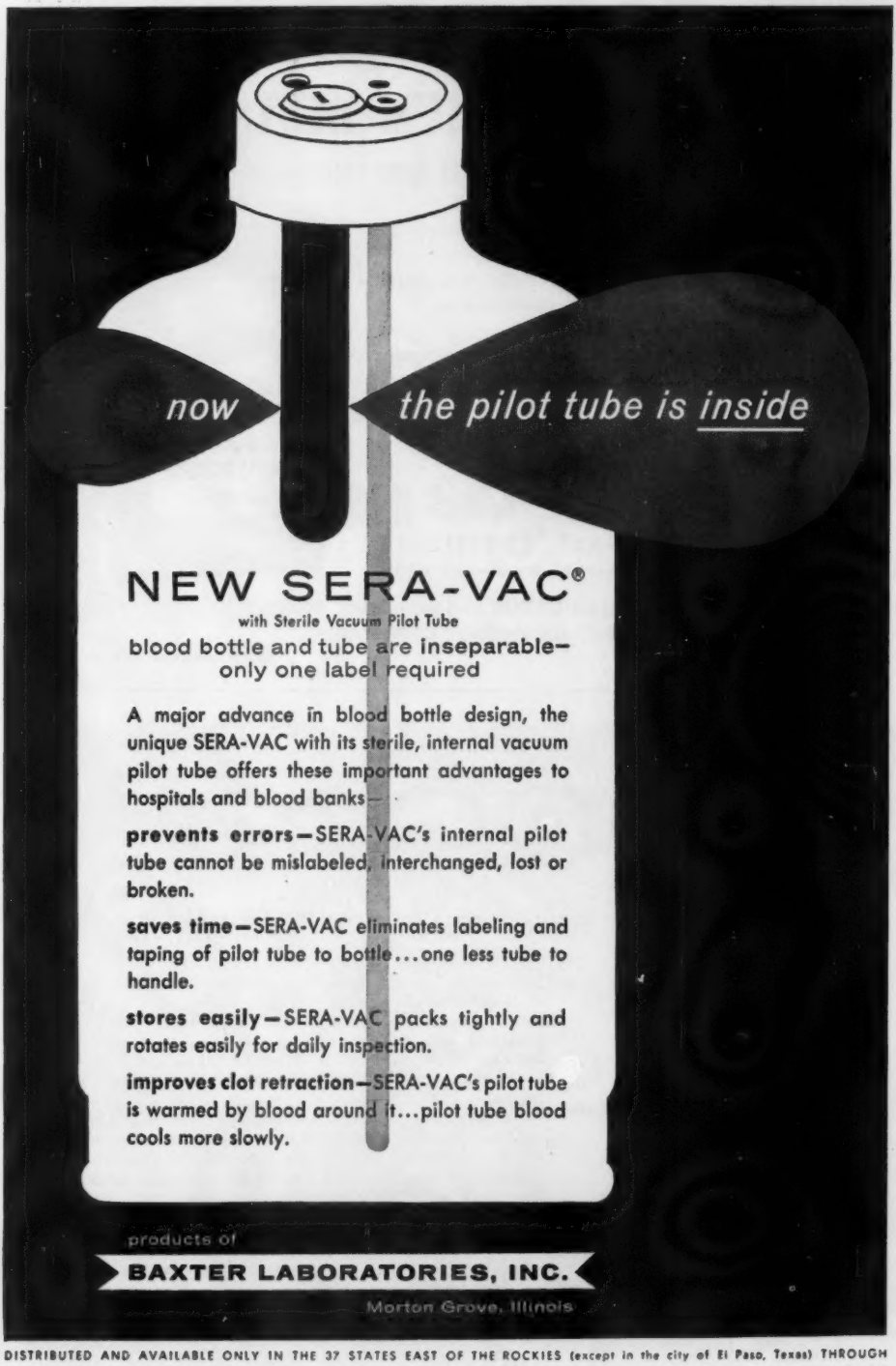
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1 "Evaluation of Drugs in the Treatment of Peptic Ulcer" by J. M. Ruffin, M.D.; D. Geyer, M.D.; J. S. Atwater, M.D., and B. G. Owen, M.D., Exhibit at A.M.A. Meeting Atlantic City, June 1955.
2 Council on Pharmacy and Chemistry, J.A.M.A. 160:389 (Feb. 4) 1956.
*REG. U. S. PAT. OFF.



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...her fears of crowds and cancer ceased to worry her[1]

case report



"40-year-old woman with overt anxiety symptoms . . . marked fear of crowds . . . phobic ideas concerning cancer. Tension, irritability, and tiredness were in evidence."

medication:

'Thorazine', 25 mg. orally, t.i.d.

response:

"Following ['Thorazine'] medication she became placid, composed and cheerful. When asked about her fears, she smiled and readily stated that they had ceased to worry her." She is now running her household for her husband and young son without difficulty.[1]

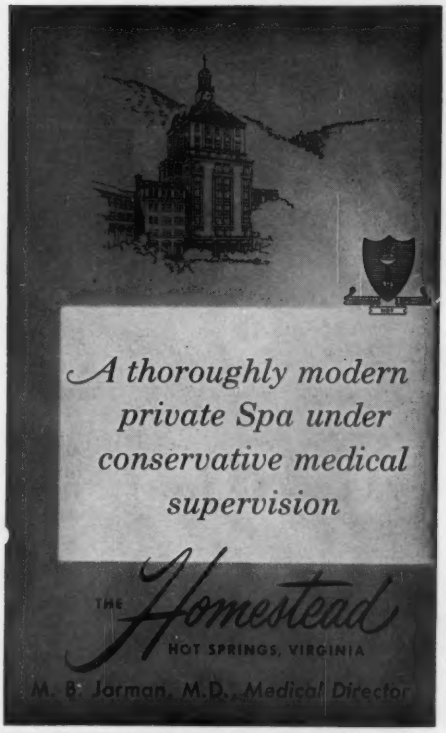
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*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

1. Silverman, M.: J. Ment. Sc. *101*:640 (July) 1955.



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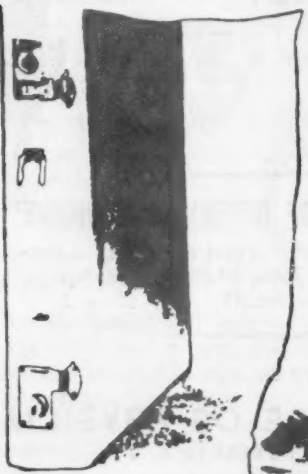
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